# FORMULATION AND EVALUATION OF MEDICATED CHEWING GUM DELIVERY OF LYMECYCLINE

*A DISSERTATION SUBMITTED TO*

**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,**
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**MASTER OF PHARMACY**

**IN**

**BRANCH I- PHARAMACEUTICS**

**Submitted by**

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# CERTIFICATE

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This is certify that the dissertation entitled "**FORMULATION AND EVALUATION OF MEDICATED CHEWING GUM DELIVERY OF LYMECYCLINE"** is a bonafide work done by Ms. S. JEYAPRIYA (Reg.No:261611301), **Department of Pharmaceutics, College of Pharmacy, Madurai Medical College** in partial fulfillment of **The Tamil Nadu Dr. M.G.R. Medical University** rules regulations for award of **MASTER OF PHARMACY IN PHARMACEUTICS in** under my guidance and supervision during the academic Year 2017-2018.

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# ACKNOWLEDGEMENT

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# CONTENTS

# CONTENTS

# LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| % | : | Percentage |
| $^0$C | : | Degree Celsius |
| λmax | : | Maximum Wavelength |
| µm | : | Micrometer |
| µg | : | Microgram |
| Abs | : | Absorbance |
| BCS | : | Biopharmaceutical classification system |
| Conc | : | Concentration |
| CDR | : | Cumulative drug release |
| cm | : | Centimeter |
| DSC | : | Differential Scanning Colorimetric |
| e.g. | : | Example |
| Etc | : | Excetra |
| FDA | : | Food & Drug administration |
| FTIR | : | Fourier transfer infrared |
| gm | : | Gram |
| GIT | : | Gastro intestinal tract |
| IP | : | Indian Pharmacopoeia |
| MCG | : | Medicated chewing gum |
| Kg | : | Kilogram |

| | | |
|---|---|---|
| L | : | Liter |
| mg | : | Milligram |
| µg | : | Microgram |
| Min | : | Minute |
| ml | : | Milliliter |
| cm | : | Centimeter |
| mm | : | Millimeter |
| nm | : | Nanometer |
| ppm | : | Parts Per Million |
| rpm | : | Revolution per Minute |
| SD | : | Standard deviation |
| UV | : | Ultra Violet |
| hrs | : | Hours |
| KBr | : | Potassium bromide |
| β-cd | : | Betacyclodextrin |
| Log | : | Logarithm |
| pH | : | Potential of hydrogen |

# CHAPTER I

# INTRODUCTION

# CHAPTER- I

# INTRODUCTION

## MOBILE DRUG DELIVERY SYSTEM

**Anatomy and physiology of oral mucosa:**

The oral mucosa can be subdivided in to two general regions, the outer vestibule and oral cavity. Microscopically the oral mucosa consists of three main layers:

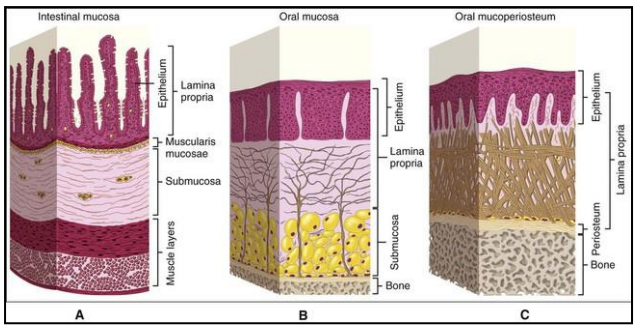
A. Oral epithelium

B. Lamina propria

C. Sub mucosa

## A. oral epithelium:

The epithelium of mouth consists of stratified, squamous epithelium, which may be either keratinized or non-keratinized, keratinized epithelium is dehydrated, mechanically in areas such as the soft palate, the floor of mouth, the lips and the cheeks tough and chemically resistant. It is found in oral cavity such as mucosa of gingival and hard palate.Nonkeratinized epithelium is relatively flexible and is found. The epithelium of the oral cavity is supported by the basement membrane. The membrane separates the epithelium from the underlying connective tissue layer. This process is represented in four morphological layers.



- Basal layer
- Prickle cell layer
- Intermediate layer
- Superficial layer

**B. lamina propria:**

The lamina propria contents a sheet of connective tissue containing collagen elastic fiber and cellular components in hydrated ground substance. It is also consists of blood capillaries and nerve fibers which serves the mucosa. The blood vessels in the laminapropria are mainly engaged in the delivery of drug moieties in systemic circulation.

**C. Sub mucosa:**

A sub mucosa may or may not be present deep to the dense layer of the lamina propria; depending on the region of the oral cavity. The sub mucosa usually contains loose connective tissue and also adipose connective tissue or salivary glands and also overlying bone or muscle within the oral cavity. Saliva is a hypotonic, watery secretion containing variable amount of mucus, enzyme, antibodies and inorganic ions. The surface of mucus membrane is constantly washed by a stream of about 0.5 to 2L of saliva daily produce in the salivary gland the chief secretion is supplied by three pairs of glands i.e. the parotid, the sub maxillary and the sublingual glands.

**NOVEL APPROACHES- BUCCAL DRUG DELIVERY SYSTEMS:**

Buccal drug delivery is one of the novel drug delivery systems. It localized the delivery to tissues of the oral cavity for the treatment of bacterial and fungal infection as well as periodontal disease. Buccal drug delivery also a safer mode

of drug delivery system and can be able to remove in case of toxicity and adverse effect. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drug from hepatic first pass metabolism.

The administration of drug through buccal route provides a direct entry of drug molecule into the systemic circulation via avoiding the first pass metabolism. it is possible bypasses of first pass effect and avoidance of pre-systemic elimination within the gastrointestinal tract. Buccal route is preferred the drugs having poor bioavailability because of high first pass metabolism. Chewing gums much more readily tolerated by the patient than tablets. Moreover, the chewing gums are able to protect the buccal surface, thus reducing infections and treating oral diseases more effectively.

## Oral mucosa:

The total area of the oral cavity is 100$cm^2$ .one third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The main role of oral mucosa is protection of tissue underlying. Lipid based permeability barriers in epithelium layer protect the tissues from fluid loss and also from the attack of harmful environmental agents like microbial toxins, antigens, carcinogens, enzymes etc. Oral epithelium proliferation time is 5-6 days. Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions. outer oral vestibule which is bounded by cheeks, lips, teeth and gingival(gums).oral cavity proper which extends from teeth and gums back to the faucets(which lead to pharynx)with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity.

**FUNCTIONS OF ORAL CAVITY:**

- It helps in chewing, mastication and mixing of food stuff.
- It is helps to lubricate the food material and bolus.
- To identify the ingested material by taste buds of tongue.
- To initiate the carbohydrate and fat metabolism.
- As a portal for intake of food material and water.

## Methods of increase drug delivery via buccal route:

## 1. Permeation Enhancers:

The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as the absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its effectively depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers. The efficacy of enhancer in one site is not some in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. The most common absorption enhancers are fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solution/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labeled dextrin’s across a tissue culture model of the buccal epithelium while

Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism.

**IDEAL REQUIREMENTS FOR DRUG PROFILE:**

1. The drug should not have any type of disagreeable taste, this can affect patient compliance.
2. The particle size of the drug should be kept below approximately 100 cm to avoid unpleasant gritty feeling during chewing.

**PHYSICO CHEMICAL PROPERTIES OF DRUG:**

- High salivary solubility.
- pH independent solubility.
- Tasteless.

**PATIENT RELATED FACTORS:**

- Non toxic to oromucosa and salivary ducts.
- Non carcinogenic.
- Should not cause tooth decay and oromucosa staining should not affect salivary flow rate.

**MECHANISM:**

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follow.

- **Changing rheology mucus:**

Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Future, saliva covering the mucus layers also hinders the absorption.

Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.

- **Increasing the fluidity of lipid bilayer membrane:**

The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by a interaction with either lipid or protein components.

- **Acting on the components at tight junctions:**

Some enhancers act as desmosomes, a major component at the tight junctions there by increases drug absorption.

- **By overcoming the enzymatic barrier:**

These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

- **Increasing the thermodynamic activity of drugs:**

Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to in-creased thermodynamic activity resulting better absorption. Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. List of some permeation enhancer are listed in table.

**Table1: Permeation Enhancers for Buccal Delivery:**

| S.no | Permeation Enhancers | s.no | Permeation Enhancers |
|---|---|---|---|
| 1. | 2, 3-Lauryl ether | 12. | Phosphatidylcholine |
| 2. | Aprotinin | 13. | Polyoxyethylene |
| 3. | Azone | 14. | Polysorbate 80 |
| 4. | Benzalkonium chloride | 15. | Polyoxyethylene |
| 5. | Cetylpyridinium | 16. | Phosphatidylcholine |
| 6. | cetyltrimethyl ammonium bromide | 17. | Sodium EDTA |
| 7. | Cyclodextrin | 18. | Sodium glycocholate |
| 8. | Dextran sulfate | 19. | Sodiumglycodeoxcholate |
| 9. | Glycol | 20. | Sodium lauryl sulfate |
| 10. | Lauric acid | 21. | Sodium salicylate |
| 11. | Lauric acid/Propylene | 22. | Sodium taurocholate |

## 2. Prodrug:

Nalbuphine and naloxone bitter drugs when administered to dogs via buccal mucosa causes excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in prod rug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds.

## 3. pH:

The in vitro permeability of acyclovir was found to be $p^H$ dependent with an increase in flux and permeability coefficient at both $p^H$ extremes (pH 3.3 and 8.8),as compared to the mid-range values (pH 4.1,5.8,and 7.0).

## ABSORPTION OF DRUG ACROSS THE ORAL MUCOSA:

The oral cavity is point of entry for oral drug formulations but their contact with the oral mucosa is brief. So in to order to take advantages of these properties or to treat the mucosa locally, this delivery system have been designed to prolong residence in this area. The total surface area available for drug absorption is quite limited being only approximately 100cm$^2$. The oral cavity is rich in blood vessels and lymphatic, so rapid onset of action and high blood levels obtained quickly.

In order to absorb orally, the drug must be dissolve in saliva. Extremely hydrophobic materials will not dissolve well and are likely to be swallowed intact unless a specialized delivery system is used to prevent them to mucosa.

### THEORY OF DRUG TRANSPORT:

Due to chewing process, most of the medications contained within the drug product are released into the saliva and are either absorbed through buccal mucosa or swallowed or absorbed through GIT as depicted in Figure 1.

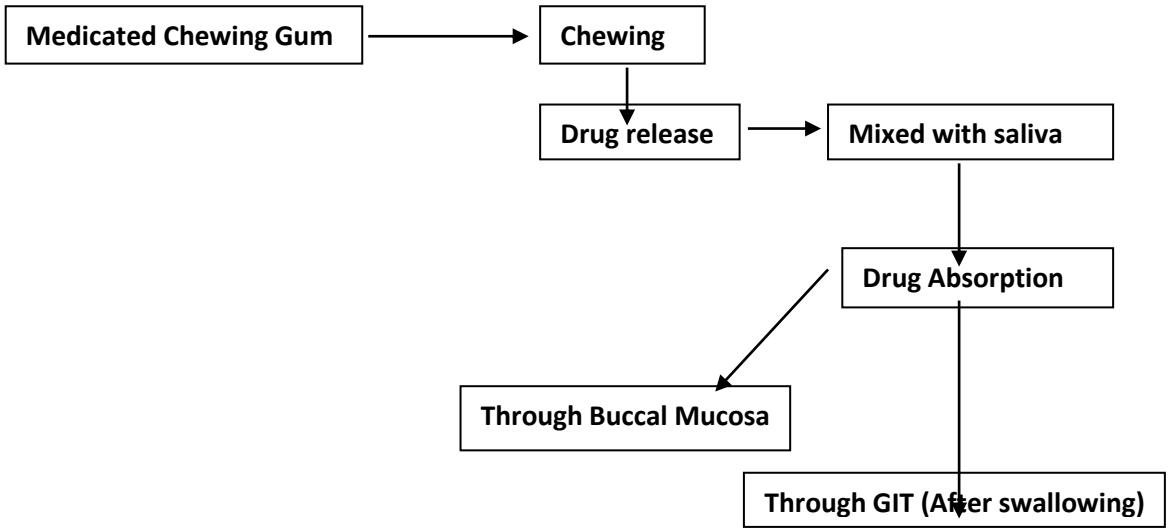



**FIGURE 1: SCHEMATIC SEQUENCE OF MECHANISM OF DRUG RELEASE FROM MCG.**

Major pathways of drug transport across buccal mucosa follow simple fickian diffusion. Passive diffusion occurs in accordance without the pH partition theory, some carrier mediated transport also observed. Equation for drug flux is:

$$J=DKp/\Delta Ce$$

Where J= Drug, D=Diffusivity, Kp = Partition coefficient and $\Delta$ Ce=Conc. Gradient.

**Mechanism of drug Transport:**

Major pathways of drug transport across the buccal mucosa follow simple fickian diffusion. Passive diffusion occurs in accordance without the pH partition theory. Some carrier mediated transport also observed. Equation for drug flux is:

$J = DKp/\Delta Ce$

Where,

J=Drug fiux

D=Diffusivity

$K_p$=partition coefficient

$\Delta C_e$=Concentration gradient

h=diffusional path length

## According to the equation, the flux may be increased by:

- Decreasing the diffusion resistance of the membrane by making it more fluid,
- Increasing the solubility of the drug in the saliva immediately adjacent to the epithelium Enhancing the lipophilicity through pro-drug modification.

- ❖ Because of the barrier properties of the tight buccal mucosa, the rate limiting step is the movement of the drug molecules across the epithelium.

**DRUGS REPORTED TO BE BEST SUITABLE IN CHEWING GUM FORMULATIONS:**

**List of commercially available medicated chewing gums:**

| S. No | Trade Mark | active ingredient | Indication |
|---|---|---|---|
| 1. | Aspergum | Aspirin | pain relief |
| 2. | Orbit white | tricalcium phosphate | dental hygiene |
| 3. | Happy dent white | sodium chloride | anti caries agent |
| 4. | Travel gum | dimenhydrinate | motion sickness |
| 5. | Super pep | dimenhydrinate | motion sickness |
| 6. | Nicorette | Nicotine | smoking cessation |
| 7. | Nicotinelle | Nicotine | smoking cessation |
| 8. | Hex it | Chlorhexidine | Antibacterial |
| 9. | Stay alert | Caffeine | cns stimulant |
| 10. | Chooz | calcium carbonate | Antacid |
| 11. | Endekay | vitamin c | Supplement |
| 12. | Go gum | Guarana | Alertness |
| 13. | Brain | DHA and CCE | Enhanced brain activity |

# CHAPTER II

# CHEWING GUM - A REVIEW

# CHAPTER-II

# CHEWING GUM - A REVIEW

- Chewing gums are mobile drug delivery system. It is a potentially useful means of administrating drugs either locally or systemically via the oral cavity.
- The medicated chewing gum has through the years gained increasing acceptance as a drug delivery system.MCG is a solid single dose preparations with a base consisting mainly of gums with are indented to be chewed but not swallowed, providing a slow steady release of the medicine contained.
- It's a novel drug delivery system containing masticator gum base with pharmacologically active ingredient and indented to use for local treatment of mouth diseases or systemic absorption through oral mucosa.
- The buccal route of drug administration also has important advantages of direct access to the general circulation and overcomes the first pass hepatic metabolism. As chewing gums are taken orally and oral route of drug delivery is the most preferred route amongst the patient and clinicians due to various advantages it offers, in recent years chewing gums are considered to be friendly oral mucosal drug delivery system.
- Children in particular may consider chewing gum as a more preferred method of drug administration compared with the oral liquids and tablets. The use of MCG is feasible in local treatment of disease of oral cavity as well as treatment of systemic conditions.

- Chewing gum is considered a valid drug delivery system that releases the active ingredient by chewing. MCG has been proven as a great delivery vehicle for nutrients and drugs.
- Chewing gum is mixture of natural or synthetic gums and resins sweetened with sugar, corn syrup, artificial sweeteners and may also include coloring agents and flavors bulking agents, softening agents, antioxidants, and glidants. MCG are prepared by different methods like direct compression method, conventional, traditional method, cooling and grinding method.
- A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded. During the chewing process the drug contained in the gum product is released from the mass into saliva and could be absorbed through the oral mucosa (or) swallowed reaching stomach for gastro-intestinal absorption.
- The first commercial chewing gum “State of Maine pure spruce gum” was marketed in 1948 in the USA. The first patent was field in 1869. The gum was intended as dentifrices but it has never been marketed. The first medicated chewing gum “As per gum” was launched in 1928. This chewing gum is still available and contains acetyl salicylic acid. Author commercially available medicated chewing gum is dimenhydrinate containing chewing gum for motion sickness.
- However, chewing gum did not gain acceptance as a reliable drug delivery system until 1978, when nicotine chewing gum became available.

- Moreover, it also benefits from advantages inherout to chewing gum such as oral care, stress relief improved focus and concentration and weight management.
- A medicated chewing gum is intended to be chewed for a certain period of time, required to deliver the dose, after which the remaining mass is discarded.
- This drug delivery system provides benefits such as pleasant taste fast onset of action and high bio availability, higher patient compliance, ready for use and fewer side effects over tablets (or) liquid formulations.
- The release of a drug from chewing gum is dependent upon its water solubility. Water soluble substances are released rapidly and completely from chewing gum and methods are available which retard their release from chewing gum to provide an extended release profile.
- Few drugs are suitable candidates for incorporation into chewing gum formulations for the intention of their systemic delivery.
- Intra oral dosage forms deliver the drug to the target sites for local or systemic drug delivery in the oral cavity include the following**.** (**Abilash mund et al.,2015**)

MCG is a novel drug delivery system containing masticatory gum base with pharmacologically active buccal ,sublingual, peritoneal, tongue (lingual) and gum (gingival).The various types of intra oral dosage forms include liquid (solution, sprays, syrups, injection etc). semi solids (ointment, pastes etc) and semisolid dosage forms (quick – dissolve and slow-dissolve tablets, sublingual tablets, lozenges, films, filaments, gums, patches, micro particles, drug delivery devices. intra oral drug delivery overcomes hepatic first pass metabolism and

promotes rapid systemic delivery with improved bioavailability with selected drugs having the required physiochemical and biopharmaceutical characteristics.

**DEFINITION:**

A medicated chewing gum is solid single dose preparation that is intended to be chewed for a certain period of time deliver the drug one active pharmaceutical ingredient and indented to use for local treatment of mouth diseases or systemic absorption through oral mucosa.

The drug product is indented to be chewed in the oral cavity for a specific period of time after which the insoluble gum base is discarded.

**BENEFITS OF CHEWING GUM:**

**ADVANTAGES:**

Medicated chewing gums offer a range of advantages.

- Chewing gum can be used without water at any time and everywhere.
- As the incorporated therapeutic agents are protected from oxygen light and water product stability is good.
- Compatible for patients having difficult in swallowing.
- Excellent for acute medication.
- Counteracts dry mouth prevents candidiasis, and caries.
- Fast and rapid onset of action.
- High bioavailability.
- Pleasant taste.
- By passes first pass metabolism and thus increases the bioavailability of drugs.
- Ready for use.

- Fewer side effects.
- Local effect.
- Improved focus and concentration stress relief.
- Duration of action is increased.
- Stimulates flow of saliva in the mouth.
- Gum does not react the stomach hence G.I.T suffers less from the effects of excipients.
- Helps whiter teeth by reducing and preventing stains.

**DISADVANTAGES:**

- Sorbitol present in MCG formulation may causes side effects like diarrhea, flatulence.
- Chewing gum has been shown to adhere to difficult degrees to enamel dentures and fillers.
- Prolonged chewing of gum may result in pan in facial muscles and ears in characters.

**CHARACTERISTIC FEATURES OF CHEWING GUM:**

- Chewing gum is a soft cohesive substance designed to the chewed without designed being swallowed.
- Modern chewing gum is composed of gum base , sweeteners, softeners, plasticizers flavors, colors and typically a hard or powdered polyol coating.
- Its texture is reminiscent of rubber because of the physical chemical properties of its polymer plasticizer and resin components which contributes to its elastic plastic, sticky, chewy characteristics.

**POLYMERS USED IN CHEWING GUM PREPARATION:**

There are various polymers co polymers cross linkers are used in the preparation of chewing gum.

**Polymers:**

Hyper linked polystyrenes cyclodextrins and its derivatives like cyclodextirns, methyl B cyclodextrins, hydroxypropyl β- cyclodextrins, poly isoprene, poly butadiene.

**Co-polymers:**

Polyvinyl alcohol, poly vinyl acetate, styrene –butadiene copolymers, vinyl acetate–vinyl laureate copolymers, copolymers of lacticacid, polyhydroxy alkonates, plasticized ethyl cellulose, polyvinyl acetate phthalate and combinations there of.

**Cross linkers:**

Cross linked poly vinyl pyrrolidone, poly methyl methacrylate.

## BASIC COMPONENTS OF MEDICATED CHEWING GUMS:

**I. Active pharmaceutical ingredient (API):**

The active pharmaceutical ingredients should be comply the following criteria. The drug should not have any type of disagreeable taste, this can affect patient compliance.

The particle size of the drug should be kept below approximately 100µm avoid unpleasant gritty feeling during chewing.

Physicochemical properties of drug such as high salivary and pH independent solubility.

Patient related factors such as nontoxic to oromucosa and salivary ducts, non carcinogenic should not cause tooth decay and oromucosa staining should not affect salivary flow rate.

**II. Gum base:**

It is an insert and insoluble nonnutritive product used as a support for the edible and soluble of the chewing gum (sugar, glucose, poly oils and flavors)other raw materials are generally grouped in the following classes:

**1. Elastomers:**

It provides elasticity, gummy texture and cohesion to the chewing gum. Natural elastomer natural rubber like latex or natural gums such as jelutong, lechicaspi,perillo, and chicle. Synthetic elastomers like polyethylene acetate, polyisobutylene and buty-1- rubber are used.

**2. Plasticizers:**

These are used to regulate cohesiveness of product. These are again divided into natural and synthetic natural plasticizers include natural rosin esters like glycerol esters or partially hydrogenated rosin, glycerol esters of polymerized esters, glycerol esters of partially dimerized rosin & pentaerythritol esters of resin. Synthetic Plasticizers include terpene Resins derived from α-pinene and or d-limonene.

**3. Resins:**

They serve two functions. One, as mastication substance and other as binding agent between elastomers and fillers, they contribute to the balance between the properties of elasticity and plasticity. Glycerol esters from pine resins are examples of natural resins. Synthetic resin polyvinyl acetate can be used. It

reduces the tendency of the gum to adhere to the teeth (detackifier) and to be divided into pieces during chewing. It has only a slight taste, its stability is good and it is available in range of different molecular weights.

**4. Emulsifiers and Fats:**

These are used to soften the mixture and give the required chewing consistency and mouth feel. Emulsifiers promote the uptake of saliva into the chewing gum during mastication. Monoglycerides, diglycerides and partly hardened vegetable and animal fat are examples. Softeners include glycerin, Lecithin, Tallow, Mono/ di/ tri-Glycerides, palmitic acid.

5. **Fillers or Textures:**

They provide the right texture, improve reasonable size of the gum lump with low dose drug for the gum base. Commonly used fillers are magnesium and calcium carbonate, Ground Limestone, Magnesium and Aluminum silicate, Clay, Alumina, Talc, Titanium Oxide & Mono /di /tri Calcium Phosphate. Antioxidants: They may be added to protect the gum base and flavors from Oxidation. Ascorbic acid, tocopherol, butylhdroxytoluene have been used.

**6. Sweeteners:**

**a. Water-soluble sweetening agents:**

Xylose, ribulose, glucose, mannose, galactose, fructose, sucrose, maltose, and invert sugar partially hydrolyzed starch, dihyrochalcones, monellin, steviosides, glycyrrhizin, and sugar alcohols such as sorbitol, mannitol, and hydrogenated starch hydrolsates.

**b. Water-soluble, artificial sweeteners:**

Soluble saccharin salts, i.e. sodium or calcium saccharin salts, cyclamate salts.

**c. Dipeptide based sweeteners:**

L-aspartic acid derived sweeteners such as Aspartame, Alitame, methyl esters of L-aspartyl-L phyenylglycerine and L-aspartyl-L 2,5-dihydrophenylglycine, L aspartyl 2, and 5-dihydro-L phenylalanine-L(1-cyclohexen) alanine.

**d. protein based sweeteners:**

Such as thaumaoccousdanielli (Thaumatin I and II) In general an effective amount of sweetener is utilized to provide the level of sweetness desired, and this amount will vary with the sweetener selected and are present in amounts from 0.0025% to 90% by weight of the gum composition.

**7. flavoring agents:**

A variety of flavoring agents are used to improve flavor in chewing gum includes essential oils, such as citrus oil, fruit essences peppermint oil, spearmint oil, clove oil and oil of wintergreen. Artificial flavoring agents can also be used.

**8. Anti –caking agent:**

An anti-caking agent such as precipitated silicon dioxide can be mixed with chewing gum composition and solid carbon dioxide prior to grinding. This helps to prevent agglomeration of the subsequently ground chewing gum particles.

**9.Antioxidants:**

An anti-oxidant such as butylated hydroxytoluene , butylatedhydroxy anisole, propyl gallate and mixtures thereof, may be included as antioxidants.

**10. Grinding agents:**

To prevent the gum from sticking to the grinding apparatus 2-8% w/w of grinding aid such as alkaline metal phosphate, an alkaline earth metal phosphate or maltodextrin can be incorporated. However practical use of these substances is limited because these substances are highly alkaline and hence would be incompatible with acidic ionizable therapeutic agents. They also tend to remain in the composition and final chewing gum tablet and thus may be problematic for therapeutic and safety point of view.

## Chewing gum types:

Chewing gum comes in a variety of flavors, shapes and sizes. There is no standard type of gum, but mostly is a small stick or wad of gum. Chewing gum is basically made by combining a water-insoluble phase with a water-soluble phase of sweeteners, flavoring and food coloring.

Today's basic types of chewing gums are

- **Bubble gum:**

  Bubble gum has property of blowing bubbles because film -forming characteristics.

- **Sugar-free gum:**

  Instead of sugar, sugar-free gum has artificial sweeteners to provide the taste .

- **Center-filled gum:**

  Center-filled gum in his center has a soft mass, Usually filled with some tasty liquid.

- **Dragee gum:**

  Dragee gum has the most popular format for chewing gum, Dragee gum is a pillow –shaped coated pellet, often packed in blister packs.

- **Medicated gum:**

  Medicated gum is a chewing gum with a purpose to introduce medicated substances into blood stream faster than pills. Based on the shapes, they are named as:

- **Stick gum:**

  Stick gum is a thin, flat, slab of gum usually in rectangular shape.

- **Ball gum:**

  The gum has shape like ball. It is one of the most popular chewing gums.

- **Ribbon gum:**

  Ribbon gum is like the stick gum, it is longer, coiled up in a cylindrical container, and the consumer tears off a piece of the size he wants.

- **Wrap gum:**

  Wrap gum and cut gum is usually in the form of a chunk, cube or cylindrical shape, depending of the machine that wraps it.

- **Tab gum:**

  Tab gum is shorter than stick gum and also thicker.

- **Tube gum:**

  Tube gum or spaghetti gum comes in a tube and gum inside tube is a very soft bubble gum.

## MANUFACTURING PROCESSES:

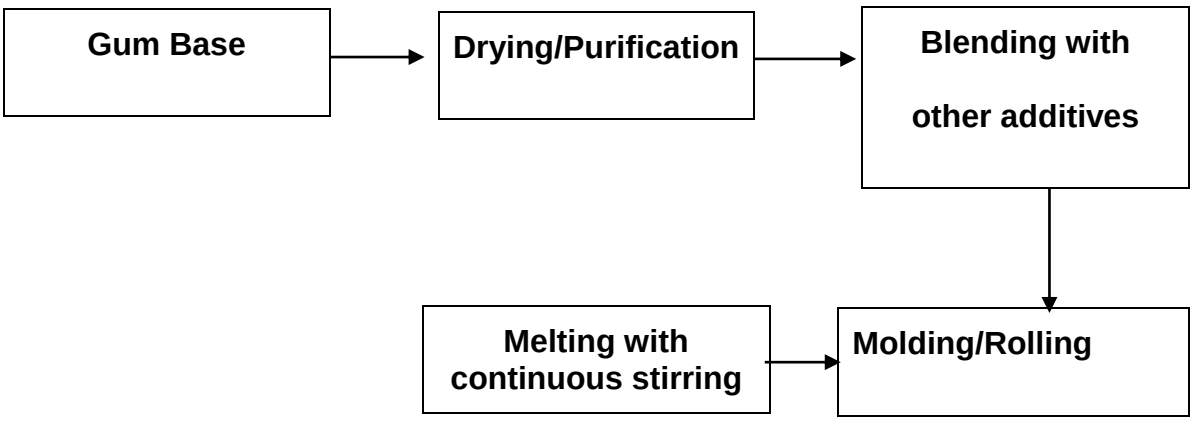
Different methods can be employed for the manufacturing of MCGs; however, these can be broadly classified into three main classes namely:

1. Conventional/ Fusion method
2. Cooling, grinding and tab letting method
3. Direct compression method

## 1. Conventional / Fusion Method:

Components of gum base are softened or melted and placed in a planetary mixer to which sweeteners, syrups, active ingredients and other excipients are added at a definite time. The gum is then sent through a series of rollers that forms into a thin, flat ribbon. During this process, a light coating of finely powdered sugar or sugar substitutes is added to keep the gum away from sticking and to enhance the flavor. In a carefully controlled room, the gum is cooled for up to 2 days. This allows the gum to set properly. Finally the gum is cut to the desired size and cooled at a carefully controlled temperature and humidity as depicted in Figure 2

.



## Limitations:

Elevated temperature used in melting restricts the use of this method for thermo labile drugs.

- Melting and mixing of highly viscous gum mass controlling of accuracy and uniformity of drug dose difficult.
- Lack of precise form, shape or weight of dosage form.
- Technology not so easily adaptable to incorporate the stringent manufacturing conditions required for production of pharmaceutical products.
- Such a chewing gum composition is difficult to form into chewing gum tablets because of their moisture content (2-8%). If attempted to grind and tablet such a composition would jam the grinding machine stick to blades, screens adhere to punches and would be difficult to compress.

## Cooling, Grinding and Tableting Method:

This method has been developed with an attempt to lower the moisture content and alleviate the problems mentioned in conventional method. The MCG base is cooled to a temperature at which the composition is sufficiently brittle and would remain brittle during the subsequent grinding step without adhesion to the grinding apparatus. The temperature required for cooling is determined in part by the composition of the MCG and is easily determined empirically by observing the properties of the cooled chewing gum composition. Generally the temperature of the refrigerated mixture is around -15ºC or lower.

Amongst the various coolants like liquid nitrogen, hydrocarbon slush use of solid carbon dioxide is preferred as it can give temperature as low as -78.5ºC, it sublimes readily on warming the mixture, is not absorbed by the chewing gum composition, does not interact adversely with the processing apparatus and does not leave behind any residue which may be undesirable or potentially hazardous. The refrigerated composition is then crushed or ground to obtain minute fragments of finally ground pieces of the composition. Alternatively, the steps of cooling the chewing gum composition can be combined into a single step. As an example, cooling the grinding apparatus itself which can be done by contacting the grinding apparatus with a coolant or by placing the grinding apparatus in a cooling jacket of liquid nitrogen or other chilled liquid, for more efficient cooling, the chewing gum composition can be pre cooled prior to cooling to the refrigeration temperature. Sometimes a mixture of chewing gum composition, solid carbon dioxide and precipitated silica is ground in a mill grinder in the first step. Additional solid carbon dioxide and silica are added to the ground composition, and the composition is further ground in the second step. This two-step grinding process advantageously keeps the chewing gum composition at a very low temperature. The presence of solid carbon dioxide also serves to enhance the efficiency of the grinding process. The same process can be made multiple by adding incorporating additional carbon dioxide and/or precipitated silica at each step. Certain additives can be added to the chewing gum composition to facilitate cooling, grinding and to achieve desired properties of chewing gum. These include use of anti-caking agent and grinding agent [25]. Once the coolant has been removed from the powder, the powder can be mixed with other ingredients such as binders, lubricants, coating agents, and sweeteners

etc, all of which are compatible with the components of the chewing gum base in a suitable blender such as sigma mill or a high shear mixer. Alternatively a Fluidized Bed Processor(FBP) can be used. The use of FBP is advantageous as it partially rebuilds the power into granules, as well as coats the powder particles or granules so obtained can be mixed with anti –adherents like talc. The mixture can be blended in an octagonal blender, screened & staged for compression.

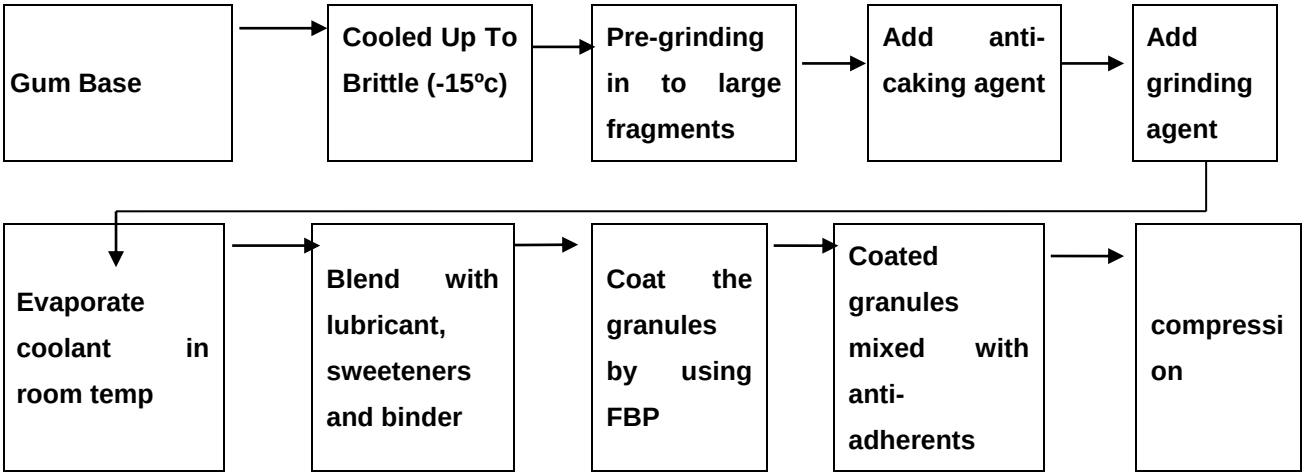
**Limitation:**

It requires equipment other than conventional table ting equipment and requires careful monitoring of humidity during the table ting process.

**3. Direct compression Method:**

The manufacturing process can be accelerated if a directly compressible chewing gum excipient is available. The limitation of melting & freezing can be overcome by the use of these.SPI pharma has developed a compatible system known as pharmagum is a mixture of polyols and of sugar with gum base, Pharmagum S consists primarily of gum base and sorbitol. Pharmagum M contains gum base, Mannitol and Isomalt. These are free following powders, which are directly compressible. It is manufactured under CGMP conditions and complies with food chemicals Codex specifications as well as with FDA, so they can be considered as “Generally regarded as safe” **(GRAS) [27].**

**Figure 3: Schematic sequence of Cooling, Grinding and Tableting Method**




## Formulation Aspects:

- Cyclodextrin complexation or solubilization technique increases aqueous solubility of drugs that are poorly water soluble.
- Increased amount of softeners and emulsifiers in gum base fasten release whereas hard gum may retard.
- A solid system of lipophilic active ingredients bound to the cat ion exchange resin permits a sustained drug delivery system.
- Microencapsulation or agglomerations are the methods to modify and control the release of active ingredient.

### Factors Affecting Release of Active Ingredient:

Several factors have been shown to affect release of drugs from chewing gum. The major determinants include the chewing time, chewing rate, aqueous solubility of the drugs, and composition of the chewing gum.

**1. Contact Time and rate:**

The local or systemic effect is dependent on time of contact of MCG in oral cavity; a survey was made to determine the length of chewing time. The mean chewing time per piece of gum was 30 to 35 min. the rate at which a subject chews gum also affects the amount of drug released. The average chewing rate is about 60 chews every minute.

**2. Inter individual variability:**

The chewing frequency and chewing intensity which affect the drug release from MCG may vary from person. In-vitro study prescribed by European Pharmacopeia suggest 60 cycles per minute chewing rate for proper release of active ingredient.

**3. Solubility of the drug:**

The saliva soluble ingredients will be immediately released within few minutes whereas lipid soluble drugs are released first into the gum base and then released slowly. Release of water soluble drug (aqueous solubility greater than 1:10) is, in general, about 75% or more during 5 min. of chewing and 90% or more during 15 min. of chewing at rate of 60 chews per minute. Drugs with aqueous solubility between 1:10 and 1:300 demonstrate up to 60% release during 10 minutes of chewing and between 50 to 90% when the gum is chewed for 15 min the release of the drug, which is only slightly water-soluble, can only be excepted to be small (less than 5%)even if the gum is chewed for 30 min.

**4. Formulation factors:**

The influence of gum base mass on drug release is depends upon changing the hydrophilic/lipophilic balance of the chewing gum formulation. The simplest way of achieving this is to increase or decrease the amount of gum base. An increase in the gum base will make the formulation more lipophilic and thus reduce the release rate of a given active substance. In principle, it is possible to manufacture products with a very low gum base content in practice a portion of chewing gum containing less than 20% gum base but will have inferior chewing properties and may not be considered a viable formulation. Instead of changing the gum base content, it is far more effective to change the release properties by adding solubilizers to the formulation. This method enables release from the chewing gum of even highly insoluble substances, e.g. Nystatine.

# CHAPTER III

# LITERATURE REVIEW

# CHAPTER-III

# LITERATURE REVIEW

- **Abin L Alex et al, [2017]** developed and evaluations of chewing gum of antiemetic drug Domperidone. Aim of present of chewing gum of domperidone was formulated to accelerate the onset of action and to improve the bioavailability so as to get quick relief from nausea and vomiting with greater patient compliance. In this study, ten formulations of domperidone were formulated as a chewing gum & best formulation was film coated. In each formulation, drug concentration remains the same the excipients concentration was varied. The prepared powder blend was evaluated for it's preformulation characteristics viz, true density, bulk density, compressibility index, angle of repose, Hardness, Friability, weight Variation, thickness, drug contet, Sickness,& in vitro dissolution analysis. Optimized formulation f10 prepared by solid dispersion showed a drug release of 97.68% and 99.9% clearly complies f10 was film coated using HPMC.

- **Kop pula Rajitha et, al, [2016]**, Formulation and evaluation of medicated chewing gum of chlorpheniramine maleate. The aim of the work was to achieve better patient compliance and improved the drug release. The medicated chewing gums are prepared by melting method. In this method different concentrations of gum base and plasticizers like glycerol and castor oil. The prepared chewing gums are evaluated for different parameters like appearance, stickiness, weight variation, drug content, hardness, thickness, in vitro drug release. Invitro release profiles of

medicated chewing gum during 30 minutes studies were found to have very good release efficacy. It was observed that as the concentration of synthetic gum base increases drug releases was decreases.

- **Rahul B.Shete* et al (2015)** formulated medicated chewing gum to prevent motion sickness. Using natural gum base for faster onset of action, easy administration, anywhere & any time, without access to water. Natural gum base prolamin extracted from wheat, showed good chewing capacity, elasticity, high water retention capacity, and three-level factorial design. Results revealed that medicated chewing gum containing 80 mg of calcium carbonate & 500 mg of gum base showed elasticity and more than 90% drug release with 16 minutes. Thus, this study suggested that both good elasticity and chew ability and availability grain can act as a potential gum base for medicated chewing gum.

- Several ingredients are now incorporated in medicated chewing gum, eg.fluoride for prophylaxis of dental carries. This review article is nicely discussed advantages, disadvantages, formulation, manufacturing process, limitation of manufacturing process, factors affecting release of active substance, quality control tests for chewing gum, significance, stability study and future trends in chewing gum drug delivery system.

- **Jyoti Ran male *et, al (2015)** developed the formulation development and evaluation of Amoxicillin based medicated chewing gum for its antibacterial activity. The aim of present study was to design and characterize medicated chewing gum for the treatment of bacterial infection using Amoxicillin trihydrate as model drug. The chewing gums

were prepared using Health in gum grade 01(HiG -01) as a directly compressible gum base developed by cafosa (S.A.U.) Spain. The effect of concentration of (Base) gum base, (release modifier) Aerosil, and (antiadherant) talc was studies. After oral administration it's rapidly abosorbed. Maximum peak plasma concentration is reached after approximately 1hr this model drug is selected for the study in order to overcome the hepatic first pass effect and there by possible. Reduction in the dose. The drug is tasteless so there bioavailability, less side effects and has short duration of action of about 1.20hr these factors make Amoxicillin trihydrate is suitable Amoxicillin for formulation of medicated chewing gum used to treat bacterial infection.

- **Padmini Iriventi et, al (2015)** Developed the formulation and evaluation of domperidone chewing gum for anti emetic activity. The aim of the work is oral drug delivery Systems time as best kind of approach for delivering various drugs but certain drugs given by oral route undergo first pass metabolism which leads to low bioavailability, making them less effective. To overcome this novel oral drug delivery Systems, ie, chewing gums were developed as an alternate for conventional oral systems. These were used for both systemic and local delivery of drugs. Domperidone, an anti emetic drugs, is poorly water soluble, to enhance it's solubility, solubilizers were used in various rations for the obtained formulations, evaluation studies were carried out. Weight Variation, drug content values were found to be within standard limit prescribed. In vitro studies were carried out using modified disintegration apparatus and all the formulations showed release between 70-90%.Ex Vivo studies were carried out using porcein

buccal mucosa & up to 60% of drug release was found. Drug excipient compatibility was studied by FTIR studies.

- **Ganesh S. Bhoi * et al (2014)** formulated and evaluation of medicated chewing gum chlorpheniramine male ate. Chewing gum is the convenient and effective means of rapidly administering chlorpheniramine male ate, as it's readily soluble, permeable and used to relieve symptoms of allergy, hay fever and common cold. This medicated chewing gum was prepared by direct compression method using gum base, sorbitol, mannitol, magnesium stearate, lecithin, menthol. This method consists of gum base & lecithin like 30-35-40% and 5-10-15% accordingly. In this formulation soya lecithin was used as a plasticizer & it was found that it acted on the drug release to some extent. When concentration of soya lecithin was increased, drug release was also found to be increased.

- **Say ed abolfazl mostafavi * et al (2014)** developed the formulation development and evaluation of metformin chewing gum with bitter taste masking. Medicated chewing gums are intended to be chewed and act either locally, absorbed via the buccal mucosa (or) swallowed with saliva. metformin hydrochloride (250 mg) with suitable sweeteners was mixed manually for 5 minutes. This mixture was spray dried; freeze dried, (or) directly mixed with chewing gum base. Glycerin, xylitol and menthol were added & the produced paste was kept in the freezer for2hto be stable. As the metformin shows bitter taste, we tried to mask this unpleasing taste using different method the releasing pattern was evaluated by using a mechanical chewing machine. The best formulation with the optimized releasing pattern, suitable physico chemical properties were identified as

well, pleasant taste were selected. Content uniformity, releasing percent, & other physico chemical properties were identified Taste, flavor, and appearance characteristics were evaluated by using a self – made questionnaire based on the hedonic test method. The chewing gum dosage content was about 86.2% the release rate of metformin chewing gum was about 70% after 5 min of mastication masking the bitter taste of drug was achieved by using acesulfame – isomalt as sweeteners and prepared it by freeze drying equipment. Metformin chewing gum had suitable appearance and appropriate invitro characteristics that follow the pharmacopeia suggestions. This chewable gum showed bitterness suppression with a suitable release rate.

- **Hem ant Ks Yadav*et, al (2014)** developed the formulation and evaluation of medicated chewing gum as antiplaque and antibacterial agent. The aim of this study was to formulate chewing gum using chlorhexidine and chitosan and to prove its antibacterial and anti plaque properties effectively at low doses of chlorhexidine. Chewing gums were prepared by using chlorhexidine and various proportions of gum base and chitosan. Hot melt technique was used to prepare chewing gums. The prepared gums were evaluated for physical parameters, compatibility studies, drug content, moisture content, stability studies & in vitro drug-release testing. The test group administered chewing gums containing chlorhexidine, with & without the polymer, while the control group administered dummy chewing gums. The volunteers were visually examined for presence (or) absence of gingival erythema, gingival edema and gingival bleeding & the antibacterial activity was assessed by the

reduction in bacterial count in the plaque samples. As the proportion of gum base was increased, an increase in hardness of the chewing gum was observed. The formulation, which contains highest concentration of chitosan, showed more in vitro release compared to other formulation, Analysis of variance revealed significant differences between subjects receiving F1 & F5 for antiplaque activity. The agent which showed a better reduction in the bacterial count and gingival index. The dose of chlorhexidine can be reduced significantly when used along with chitosan. chitosan containing chewing gum has a greater antibacterial effect compared with gum containing only chlorhexidine.

- **Ritesh Kumar et,al (2014)** Reviewed on chewing gums, chewing gums are mobile drug delivery systems. Unlike chewable tablets medicated gums are not supposed to be swallowed & may be removed from the site of application without resort to invasive means & medicated chewing gum MCG is solid, single dose preparation. As for as patient convenience is concerned it's discrete and easy administration without Water promotes higher compliance. Since it can be taken any were, a chewing gum formulation is an excellent choice for acute medication. The ad vantages for children and for patients who find swallowing tablets difficult are obvious. The medicated chewing gums are solid, single dose preparations with a base consisting mainly of gums that are intended to be chewed, but not swallowed. They contain one (or) more active substances, which are released by chewing &are intended to be used for local treatment of mouth diseases (or) systemic delivery after absorption through the buccal mucosa. This concept is supported by statements that chewing sugar free

gum can help reduce the risk of dental caries (cavities).the objective of this systematic study is to appraise existing evidence concerning a possible therapeutic effect of sugar free chewing gum for patients. MCG represents the newest system with potential uses in pharmaceutical, over the counter medicines and nutraceuticals.

- **Paresh Mohan * et al (2013)** developed the formulation and evaluation of medicated chewing gum of metaclopramide. A new attempt has been made to formulate new chewing gum device for metaclopramide in the form of tablet, by direct compression using conventional pharmaceutical equipment. Different gum with varying concentration of plasticizers like glycerol and castor oil were formulated. Better consistency of formulation and faster release of drug in saliva was obtained with glycerol F(3) and castor oil F(2) But castor oil show optimum result against test showed 85% of drug absorbed within 15 min when available to the buccal mucosa at pH 5.5, Hence, metaclopramide chewing gum can be considered as a better formulation for the buccal drug delivery system, in which drug is absorbed buccally and reaches the systemic circulation via jugular vein.

- **Dr. Abolfazl Aslani, * et al (2012)** developed the design, formulation and evaluation of nicotine chewing gum. Nicotine replacement therapy (NRT) can help smokers to quit smoking. However, the bitter taste of such gums may compromise their acceptability by patients. This study was, therefore, designed to develop 2and 4mg nicotine chewing gums of pleasant taste, which satisfy the consumers the most. Most formulations released 79-83% of their nicotine content within 20minute. Nicotine containing sugar coated gums in which aspartame as sweetener and cherry and eucalyptus as

flavoring agents were incorporated had optimal chewing hardness, adhering to teeth, and plumpness characteristics as well as the most pleasant taste and highest acceptability to smokers nicotine gums of pleasant taste may, therefore, be used as NRT to assist smokers quit smoking.

- **Sabera Khatun * et al (2012)** reviewed medicated chewing gum: An unconventional drug delivery system. It's considered to be a potential and convenient modified release drug delivery system which can be used in pain relief medication, smoking cessation, travel illness, freshening of breath, prevention of dental caries, alleviation of xerostomia, vitamin (or) mineral supplementation etc. This formulation offers both local and systemic effects and has a range of advantages over conventional oral solid dosage forms. Medicated chewing gum has drawn attention to the researchers as potential drug delivery system and it could be a commercial success in near future.

- **Swami N.G.N* et al (2012)** developed the formulation and characterization of medicated chewing gums of Dextromethorphan Hydro bromide. Dextromethorphan hydro bromide chewing gum formulations were made employing pharmagum M as the base with an aim to overcome the first pass effect, reducing the risk of overdosing, ease of administration and for achieving faster systemic absorption. The prepared medicated chewing gums were 7evaluated for various precompression and post compression parameters. The formulations were found to be stable in respect to physical parameters and no significant deviations were seen in respect to in vitro drug release characteristics.

- **Abolfazl Aslani *et al (2012)** developed the design, formulation and evaluation of caffeine chewing gum. In other dosage forms caffeine increases alertness and decrease fatigue. Aim of this study to design a new formulation of caffeine chewing gum with desirable taste and assess its physico chemical properties. It is prepared by softening of gum bases and the mixing with other formulation ingredients. After making all formulations, choose the best formulation in organoleptic properties. The gum released about 90% of their own drug content after 30 minutes. In this study, caffeine gums with suitable and desirable properties (good taste& satisfactory release) were formulated.

- **Bhaskar D.Ingole*et al (2012)** reviewed, chewing gum: A mobile drug delivery system. It's a potentially useful means of administering drugs either locally (or) systemically via the oral cavity. The medicated chewing gum has through the years gained increasing acceptance as a drug delivery system. Several ingredients are now incorporated in medicated chewing gum; (e.g.) fluoride for prophylaxis of dental caries, chlorhexidine as local disinfectant, nicotine for smoking cessation, aspirin as an analgesic, as caffeine as stay alert preparation. MCGs are solid, single dose preparation with a base consisting mainly of gums that are intended to be chewed but not swallowed. The contain one (or) more active substances which are released by chewing and are intended to be used for local treatment of mouth diseases (or) systemic delivery after absorption through the buccal mucosa.

- **Farhad Mehta*et al (2011)** developed the formulation and characterization of medicated chewing gum drug delivery of

diphenhydramine hydrochloride. The release of a drug from chewing gum is dependent upon its water solubility. Water soluble substances are released rapidly and completely from chewing gum and methods are available which retard their release from chewing gum and require special formulation techniques to produce satisfactory release profile. Studies evaluating the potential application of medicated and non-medicated chewing gum in the oral cavity are described. Specific examples of the use of chewing gum as a delivery system for dental health, smoking cessation and antifungal therapy are cited. Few drugs are suitable candidates for the intention of their systemic delivery. Know-how derived from the development and manufacture of already existing medicated & non-medicated chewing gum, supplemented with today's knowledge of the principles of pharmaceutical formulation, constitute the basis for the development of the medicinal chewing gum of tomorrow.

- **Vipul P.Patel *et, al (2011)** reviewed on medicated chewing gum. Chewing gums are mobile drug delivery systems. It's a potentially useful means of administering drugs either locally (or) systemically via, the oral cavity the medicated chewing gum has through the year gained increasing acceptance as a drug delivery system.

- **M.Bolan *et al (2008)** developed the erosive effects of acidic center-filled chewing gum on primary and permanent enamel. The aim of this study was to evaluate the erosive potential of acidic filling of chewing gum in primary and permanent enamel. Eighty enamel blocks (40 permanent and 40 permanent teeth) were used and randomly distributed into eight groups. All groups showed a significant decrease in surface micro hardness. There

was a statistically significant difference between D1, D2, D3, and D4, regarding the concentration, then the diluted acid content was associated with a greater decrease in micro hardness. It's concluded that the acidic filling of a chewing gum reduced the micro hardness of primary and permanent enamel.

- **Alasdair McGowan * et al (2006)** developed the pharmacokinetics & pharamacodynamics of the tetracycline's including glycyclines the pharmacokinetics of tetracycline's and glycyclines are described in three groups. Groups1, the oldest group represented by tetracycline, oxytetracyclines, chlortetracycline, demeclocycline, lymecycline, methacycline and rolitetracycline is characterized by poor absorption after food. Group2, represented by deoxycycline, is more reliably absorbed orally, while group3, represented by the glycycline. Tigecycline is inject able only, with an improved antibacterial spectrum compared with the tetracycline's. Though incompletely understood, the pharamacodynamic properties of the tetracycline's & glycylcyclines.

# CHAPTER IV

# AIM OF WORK

# CHAPTER - IV

# AIM OF WORK

- Oral drug delivery systems have proven time as best kind of approach for delivering various drugs. Oral route has been the most commonly adopted and most convenient route for the drug delivery.
- Conventional oral drug delivery systems are tablets and capsules. But they have certain disadvantages like some drugs cause gastric irritation, some undergo first pass metabolism and difficulty in swallowing for those suffering Dysphagia.
- First pass metabolism which leads to low bio availability, making them less effective. To overcome these Novel oral drug delivery systems, i.e. ., chewing gums were developed as an alternate for conventional oral systems. These were used for both systemic & local delivery of drugs. These systems have benefits like increased patient compliance, increased bioavailability & self administration.
- The aim of present study was to design and characterize medicated chewing gum for the treatment of bacterial infection using lymecycline as model drug. Lymecycline is an Antibacterial agent.
- It prevents spreading of the infection & the growth of bacterial mainly used in conditions such as chronic bronchitis, Lyme disease, dental infections and acne.
- After oral administration it’s rapidly absorbed. Maximum peak plasma concentration is reached after approximately 2 hr this model drug is

selected for the study in order to overcome the hepatic first pass effect and there by possible reduction in the dose.

- Lymecycline has higher oral bioavailability, less side effects and has quick onset of action these factors make lymecycline is suitable candidate for formulation of medicated chewing gum used to treat bacterial infection. So it's a drug of choice in Dental infections (Infections in (or) around the mouth)

- Lymecycline is a broad spectrum antibiotic used in mouth disease. It's usually administered orally. It has first pass metabolism and show a very poor dissolution rate in order to overcome this problem by preparation of medicated chewing gum.

- Lymecycline inhibits the cell growth by inhibits the cell growth by inhibiting translation (protein biosynthesis inhibitors); Tetracycline antibiotic. The drug binds reversibly to the 30s subunit of the bacterial ribosome, thereby blocking access of the amino acyl/-- RNA to the mRNA – ribosome complex at the acceptor site. By, this mechanism, bacterial protein synthesis/ is inhibited.

- To overcome all the drawbacks development of MCG of Lymecycline

  improves the patient compliance.

# CHAPTER V

# PLAN OF WORK

# CHAPTER- V

# PLAN OF WORK

**STEP: I**

**PRE-FORMULATION STUDIES:**

Standard curves for Lymecycline:

a. Determination of λ max of Lymecycline in Phosphate buffer pH 6.8.

b. Calibration curve for the Lymecycline at max in Phosphate buffer pH 6.8.

**STEP: II**

**DRUG- POLYMER INTERACTION STUDIES:**

Fourier Transform Infrared Spectroscopic (FT-IR) Studies.

**STEP: III**

**PREPARATION OF MEDICATED CHEWING GUM BY MELTING METHOD:**

(Conventional/ traditional method):

Chewing gums are prepared by melting a gum base at a temperature of 60-70$^{o}$c until it softens. To this molten mass add liquid glucose & glycerol and mix well. Remove the mass from heat and add all other ingredients, mix well, rolled in calcium carbonate powder, cut into required size & shape.

**STEP: IV**

**CHARACTERIZATION OF LYMECYCLINE MEDICATED CHEWING GUM:**

**:** Determination of production yield

- Determination of drug content.

- Solubility profile.
- Invitro release studies of Lymecycline chewing gum.
- Kinetics of drug release.
- Stability studies.

**STEP: V**

**SELECTION AND EVALUATION OF BEST FORMULATION:**

- Production yield.
- Solubility profile.
- In-Vitro drug release studies
- Release kinetics.
- Stability studies.

**STEP: VI**

**EVALUATION OF BEST FORMULATION:**

- Release kinetics.
- Fourier transforms infrared spectroscopy (FT-TR) & Stability analysis.
- Differential scanning calorimetric (DSC)
- Stability Study
- Drug content
- In Vitro drug release studies

**STEP: VII**

**FORMULATION OF LYMECYCLINE CHEWING GUM:**

Lymecycline chewing gums are formulated by melting method. Required quantity of synthetic gum base was taken into a china dish and melted taken into a china dish and melted at a temperature of 60-70$^{o}$c until it softens. To this molten mass add required quantity of liquid glucose and glycerol mix it. Remove the mass from the heat add all other ingredients mixed well & rolled in calcium carbonate powder, cut into six and shape.

**STEP: VIII:**

**EVALUATION OF MEDICATED CHEWING GUM:**

a. **Compatibility studies:**
   - ❖ Fourier- transform Infra red spectroscopic (FTIR) studies

b. **Pre Compressional evaluation:**
   - ❖ Drug content

c. **Pre compressional evaluation of medicated chewing gum:**
   - ❖ General appearance.
   - ❖ Length of chewing gum.
   - ❖ Weight variation
   - ❖ Drug Content
   - ❖ Invitro release studies

d. **Comparison of Invitro release of Lymecycline chewing gum with pure drug lymecycline.**

# CHAPTER VI

# MATERIALS AND EQUIPMENTS

# CHAPTER- VI

# MATERIALS AND EQUIPMENTS

| S.NO | POLYMER/ EXCIPIENTS | MANUFACTURER |
|---|---|---|
| 1. | Lymecycline | Gift sample from Madras Pharmaceuticals, Chennai, India |
| 2. | Poly Vinyl acetate | Gift sample from Madras Pharmaceuticals Chennai, India |
| 3. | Betacyclodextrin | Central Drug House (P) Ltd, New Delhi, India |
| 4. | Polyethylene glycol | Pharma Fabrikon, Madurai India |
| 5. | Poly Vinyl alcohol | Pharma Fabrikon, Madurai India |
| 6. | Cross Povidone | Pharma Fabrikon, Madurai India |
| 7. | Glycerol | Scientific universal appliances |
| 8. | Sucrose | Scientific universal appliances |
| 9. | Calcium Carbonate | Scientific universal appliances |
| 10. | Mannitol | Scientific universal appliances |
| 11. | Aspartame | Madras Pharmaceuticals |
| 12. | Flavor | Scientific Universal appliances |

# EQUIPMENTS

| S.NO | POLYMER/ EXCIPIENTS | MANUFACTURER |
|---|---|---|
| 1. | Electronics weighing balance | A & D Company HR 200, Japan |
| 2. | UV Visible Spectrophotometer | Shimadzu, Japan |
| 3. | Hot air oven | Rands Instruments Chennai, India |
| 4. | Digital Scanning Calorimeter | DSC 60 Shimadzu |
| 5. | Fourier Transform Infrared Spectrophotometer | Shimadzu, Japan |

# CHAPTER VII

‘

## DRUG PROFILE

# CHAPTER- VII

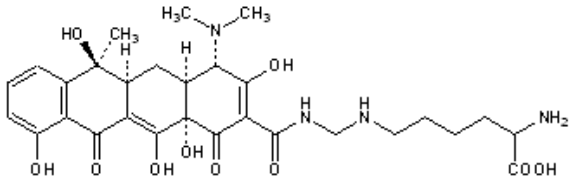
# DRUG PROFILE

## LYMECYCLINE:

### Synonym:

Mucomycin, Limeciclina, Tetracycline –L- Methylenelysine

### Structural Formula:



### Empirical Formula:

$C_{29}H_{38}N_4O_{10}$

### Chemical Name:

(2S)-6- ((((Z) - ((4s, 4as, 5as, 6s, 12, as)-4

(Dimethylamino)-6, 10, 11,12a- tetra

Hydroxyl-6- methyl -1, 3, 12 – trioxo-4,4a

5,5a-tetrhydro tetracen-2- yildene)

-hydroxy methyl) amino) methyl amino)-2-amino hexanoic acid.

### Chemical Data:

Boiling Point : $840.5^0$c at 760mm Hg

Melting Point : Above $200^0$ 6>139$^o$c

| | | |
|---|---|---|
| Solubility Profile | : | Very Soluble in Water<br>Slightly Soluble in ethanol (96%) &<br>Practically insoluble in methylene chloride, ether, chloroform. |
| Description | : | Yellow, hygroscopic Powder |
| Bio-availability | : | 100% (Oral) |
| Protein Binding | : | 80-90% |
| Half – life | : | (10 hours) 7-14 hours |
| PH range | : | At all the physiological PH Values |
| Nature | : | Yellow, hygro scopic powder |
| Density | : | 1.53 |
| Flash Point | : | 462.1$^{o}$c |
| Log P | : | (Octanol/ Water) Partition Coefficient-3.2 |
| Refractivity | : | 154.51 $m^3$ $Mol^{-1}$ |
| Polari ability | : | 62.88 A$^{o}$3 |
| Number of rings | : | 4 |
| Excretion | : | Kidney |
| Storage | : | Amber Vial, -86$^{o}$c Freezer, under inert atmosphere |

**Identification:**

λmax at 267 nm in UV spectrophotometer

**Pharmacodynamic Properties:**

Lymecycline, is a tetracycline bread spectrum antibiotic. It is approximately 5000 times more soluble than tetracycline base and is unique amongst tetracycline's in that its absorbed by the active transport process across the intestinal wall, making use of the same fast and efficient mechanism by which carbohydrates are absorbed. It inhibits cell growth by inhibiting translation.

**Mechanism of action:**

Lymecycline inhibits cell growth by inhibiting translation. It binds to the 30s ribosomal subunit & prevents the amino-acyl tRNA from binding to the A site of the ribosome. The binding is reversible in nature. Lymecycline is lipophilic and can easily pass through the cell membrane (or) passively diffuses through porin channels diffuses through porin channels in the bacterial membrane cells become resistant to lymecycline by at least two mechanisms: efflux and ribosomal protection. In efflux, a resistance gene encodes a membrane protein that actively pumps lymecycline out of the cell. This is the mechanism of action of the tetracycline resistance gene on the artificial plasmid PBR 322. In ribosomal protection, a resistance gene encodes a protein which binds to the ribosome and prevents lymecycline from acting on the ribosome.

**Pharmacokinetics:**

**Absorption:**

Absorption is rapid, effective plasma levels are reached within the first hour following drug intake:

The peak plasma level is reached within 3 to 4 hours after, oral administration. Concurrent milk in take has not been shown to significantly modify the absorption of lymecycline.

**Distribution:**

Oral administration of 300 mg, in the adult give rise to:

- A peak plasma level of 1.6 to 4 mg/ml.
- A highly variable residual concentration (0.29 to 2.19 mg/ml)
- A plasma half life of approximately 10 hours.

Repeated administration results in a steady mean plasma concentration between 2.3 and 5.8 mg/ml. Wide intra and extra cellular diffusion, under normal dosage conditions, results in effective concentrations in most body tissues and fluids, and notably in the lungs, bones, muscles, liver, bladder, prostate, bile and urine.

**Excretion/ elimination:**

The product is principally excreted in urine and secondarily in the bile. About 65% of the administered doses are eliminated within 48 hours.

**Dosage forms:**

Capsules 300 mg, 408 mg

**Therapeutic Indications:**

Lymecycline is primarily indicated in conditions like acne vulgaris, Amoebiasis, Bacterial infections, Endocarditis, Pneumonia, Rickettsiae, Syphilis, & can also be given in adjunctive therapy as an alternative drug of choice in acute sinusitis, chronic bronchitis, soft tissue infections.

**Dose:**

408 mg twice a day

**Adverse effects:**

The severe (or) irreversible adverse effects of lymecycline, which given rise to further complications, include. Increased blood urea nitrogen, Azotemia, Acidosis, Azotemia. Lymecycline produces potentially life- threatening effects which include anaphylaxis, acute hepatic dysfunctioning which are responsible for the discontinuation of Lymecycline therapy. Nausea, Diarrhea, stomach pain.

**Preparations:**

Capsules

**Storage:**

Store below 25$^{o}$c protect from sunlight.

**Contra- indications:**

Lymecycline is contra-indicated in conditions like systemic lupus erythematosus.

**Brand Names**

Dam elium (Act avis group)

Limeclin (Mediderm)

Tetralisal (Gal derma)

Tetraysal

# CHAPTER VIII

# EXCIPIENTS PROFILE

# CHAPTER- VIII

# EXCIPIENTS PROFILE

## POLY VINYL ALCOHOL

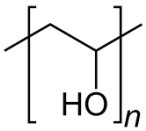
### Synonym:

- airvol
- Elvanol
- Gohsenol

### Empirical Formula:

$(C_2H_4O)$ n 20000-200000

### Structural Formula:




### Functional Category:

- Coating agent
- Lubricant
- Stabilizing agent
- Viscosity- increasing agent.

### Applications:

- Poly vinyl alcohol is used primarily in topical pharmaceutical and ophthalmic formulations.
- It's use as a stabilizing agent for emulsions

**Description:**

Ploy vinyl alcohol occurs as odorless, white to cream colored granular powder.

**Solubility:**

Soluble in water, slightly soluble in ethanol, insoluble in organic solvents.

**Storage Conditions:**

- Poly vinyl alcohol is stable when stored in a tightly sealed container cool, dry place.
- Aqueous solutions are stable in corrosion- resistant sealed container.

**Safety:**

- PVA is generally considered a non-toxic material.
- It's non- irritant to the skin and eyes at concentrations up to 10% concentrations up to 7% are used in cosmetics.

**Handling Precautions:**

- Protection & gloves recommended.
- PVA dust may be an irritate on inhalation.
- Handle in well ventilated environment.

# ASPARTAME

**Synonyms:**

- Aspartyl Phenyl amine methyl ester
- Nutra Sweet
- Pal Sweet
- Canderel
- Equal
- Pal Sweet diet

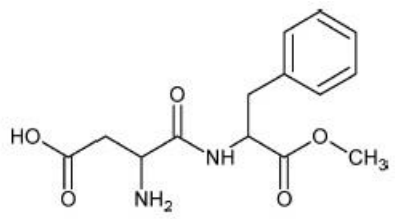
**Chemical Name:**

- N-a-L- Aspartyl- L- Phenyl -alanine 1-methyl ester

**Empirical formula and molecular weight:**

$C_{14}H_{18}N_2O_5$ 294.31

**Structural Formula**




**Functional Category:**

- Sweetening agent

**Description:**

Aspartame occurs as an off white, almost odorless, crystalline powder with an intensely sweet taste.

**Density: (true)**

1.347 g/cm$^3$

**Melting Point:**

246-247$^o$c

**Solubility:**

Slightly soluble in ethanol (95%); sparingly soluble in water. At 20$^o$c the solubility is 1% acidic PH, e.g., at PH1 and 20$^o$c solubility is 10% W/v.

**Stability and Storage Conditions:**

- Aspartame is stable in dry conditions. In the presence of Moisture, hydrolysis occurs to form the degradation products L-asparty1-L-Phenylalanine & 3 benzyl -6- car boxy methyl -2, 5- diketopiperazine. A third- degradation product is also known, B-L-aspartyl- L Phenylalanine methyl ester.
- Aspartame degradation also occurs during prolonged heat treatment losses of aspartame may be minimized by using processes that employ high temperatures for a short time followed by rapid cooling.
- The bulk material should be stored in a well closed container, in a cool, dry place.

**Method of manufacture:**

Aspartame is produced by coupling together L-phenylalanine (or L-Phenyl alanine methyl ester) and L- aspartic acid, either chemically (or) enzymatic ally. The former procedure yields both the sweet a- aspartame from which the aspartame has to be separated and purified. The enzymatic process yields only aspartame.

**Handling precautions:**

Observe normal precautions appropriate to the circumstances and quantity of material handled.measures should be taken to minimize the potential for dust explosion.eye protection is recommended.

**Applications:**

- Intense sweetening agent in beverage products,food products and table-top sweeteners and in pharmaceuticalpreparations including tablets,powder mixes and vitamin preparations.
- Therapeutically,aspartame has also been used in the treatment of sickle cell anaemia.

## MANNITOL

**Synonyms:**

- Cordycepic acid, Manna Sugar, D- Mannite, Mannite, Mannogem,Pearlitol.

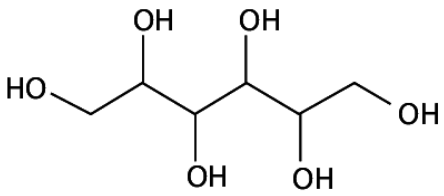
**Chemical Name:**

D- Mannitol

**Empirical Formula & Molecular Weight:**

$C_6 H_{14} O_6$ 182.17

**Structural Formula:**




**Functional Category:**

Diluents, Diluents' for lyophilized preparations, sweetening agent, tablet and capsule diluents; tonicity agent.

**Description:**

Mannitol is D- Mannitol. It's a hexahydric alcohol related to mannose and is isomeric with sorbitol.

- Mannitol occurs as a white, odorless, crystalline powder (or) free- flowing granules. It has a sweet taste, approximately as a sweet as glucose & half as sweet as sucrose, and imparts a cooling sensation in the month. Microscopically, it appears as orthorhombic needless when crystallized from alcohol. Mannitol shows polymorphism.

**Density: (True)**

1.514 g/$Cm^3$

**Density: (tapped)**

166-168$^oc$

**Solubility:**

| Solvent | Solubility at 20$^oc$ |
|---|---|
| Alkalis | Soluble |
| Ethanol (95%) | 1 in 83 |
| Ether | Practically insoluble |
| Glycerin | 1 in 18 |

**Stability and storage conditions:**

Mannitol is stable in the dry state and in aqueous solutions. In solution, Mannitol is not attacked by cold, dilute acids or alkalis or by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Millard reactions.

- The bulk material should be stored in a well closed container in a cool, dry place.

**Incompatibilities:**

Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum copper and iron.

**Method of manufacture:**

Mannitol may be extracted from the dried sap of manna & other natural sources by means of hot alcohol (or) other natural sources by means of hot

alcohol (or) other selective 501 vents. It's commercially produced by the catalytic (or) electrolytic reduction of mono saccharides such as mannose and glucose.

**Safety:**

Mannitol is a naturally occurring sugar alcohol found I animals and plants; it's present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities.

**Handling precautions:**

Observe normal precautions appropriate the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended.

**Applications in pharmaceutical formulation:**

- Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it's primarily used as a diluents (10-90% W/w) in tablet formulations, where it's of particular value since it's not hygroscopic and may thus be used with moisture- sensitive active ingredients/
- Mannitol may be used in direct compression tablet applications, for which the granular and spray dried forms are available, (or) in wet granulations. Granulations containing mannitol have the advantage of being dried easily,
    - Mannitol is also used as diluents in rapidly dispersing oral dosages forms.
    - It's used in food applications as a bulking agent.

# POLY ETHYLENE GLYCOL 4000

## Synonyms:

- Carbowax
- Carbowax Sentry
- Lipoxol
- Pluriol E
- Poly oxy ethylene glycol

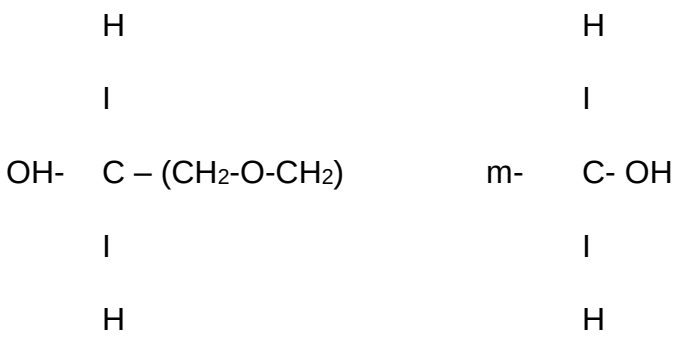
## Empirical Formula:

$H(OCH_2CH_2)_nOH$

## Molecular weight:

3000-4800 g/Mol

## Structural Formula:



## Functional Category:

Ointment base, Plasticizer, Solvent, Suppository base, tablet & capsule lubricant.

**Description:**

- Polyethylene glycol as being an addition polymer of ethylene oxide and water. Poly ethylene glycol grades 200-600 are liquids, grades 1000& above are solids at ambient temperatures.
- Liquid grades (PEG 200-600) occur as clear, colorless (or) slightly yellow colored, viscous liquids. They have a slight but characteristic odor. Grads of PEG 6000& above are available as free flowing milled powders.

**Pharmacopeial Specifications**

**Solubility:**

- All grades of polyethylene glycol are soluble in water & miscible in all proportions with other polyethylene glycols (after melting, if necessary)
- Liquid poly ethylene glycols are soluble in acetone, alcohols, benzene, glycerin & glycols.
- Solid poly ethylene glycols are soluble in acetone, dichloromethane, ethanol (95%) & methanol they are slightly soluble in aliphatic hydrocarbons & ether, but insoluble in fats, fixed oils, & mineral Oil.

**Surface Tension:**

44 mN/m (44 dynes/cm)

| | | |
|---|---|---|
| Density | : | 1.080 ($g/cm^3$) |
| Freezing Point | : | 53-59 |
| Hydorxyl Value | : | 25-32 |
| Viscosity | : | 110-170 |

**Stability and storage conditions**:

- Polyethylene glycols are chemically stable in air & in solution, although grades with a molecular weight less than 2000 are hygroscopic.
- PEG should be stored in well- closed containers in a cool, dry place. Stainless steel, aluminum, glass (or) linted steel containers, are preferred for the storage of liquid graders.

**Method of manufacture:**

- Polyethylene glycols are Condensation polymers formed by the reaction of ethylene oxide & water under pressure in the presence of a catalyst.

**Safety**:

- Nontoxic & Non Irritant materials.
- Oral administration of large quantities of PEGs can have a laxative effect.
- Topical preparations containing poly ethylene glycols.
- Should therefore be used cautiously in patients with renal failure, extensive burns (or) open wounds.
- The who has set an estimated acceptable daily intake of polyethylene glycols at up to 10mg/kg body weight.

**Handling Precautions:**

Should observe normal precautions appropriate to the circumstances and quantity of material handling protection is recommended.

**Applications:**

- PEGs are widely used in a variety of pharmaceutical formulations including parental, topical, ophthalmic, oral & rectal preparations.
- It has been used experimentally in biodegradable polymeric matrices used in controlled release systems.
- The poly ethylene glycols are water soluble & are easily removed from the skin by washing, making them useful as ointment bases.

# SUCROSE

**Synonyms:**

- Beet sugar
- Cane sugar
- Refined Sugar

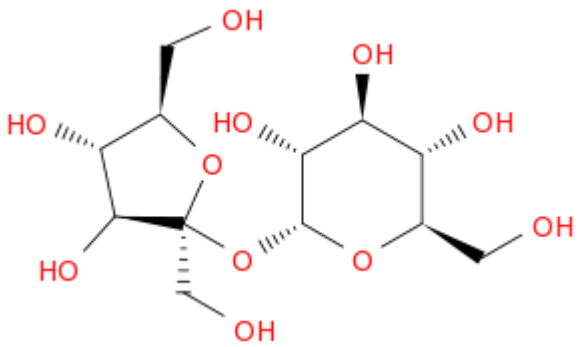
**Empirical formula:**

$C_{12}H_{22}O_{11}$

**Chemical Name:**

B-D- Fructofuranosyl – a- D- glucopyranoside

**Structural formula:**




**Functional Category:**

- Base for medicated confectionery.
- Coating agent
- Granulating agent
- Sugar Coating adjacent
- Suspending agent
- Tablet binder

**Description:**

1. Sucrose is a sugar obtained from sugar cane (SaccharumofficinarumLinne) (FAM: Graminae) sugar beet (Beta Vulgar is Linne) (Fam. Chenopodiaceae), & other sources. It contains no added substances. Sucrose occurs as colorless crystals, as crystalline masses (or) as a white crystalline powder, it's a odorless & has a sweet taste.

**Pharmacopeial specifications Solubility:**

| | | |
|---|---|---|
| Solvent | : | Solubility at 20$^{o}$C unless otherwise stated |
| Chloroform | : | Practically Insoluble |
| Ethanol | : | 1 in 400 |
| Ethanol (95%) | : | 1 in 170 |
| Water | : | 1 in 0.5 |
| | | 1 in 0.2 at 100$^{o}$c |

**Typical Properties:**

| | | |
|---|---|---|
| Density (bulk) | : | 0.93 g/cm$^3$ |
| | | (Crystalline sucrose) |
| | | 0.60 g/cm$^3$ (Powdered sucrose) |

**Density (tapped):**

- 1.03 g/cm$^3$ (crystalline sucrose)
- 0.82 g/cm$^3$ (Powdered Sucrose)

**Density (true):**

- 1.6 g/$cm^3$

**Density (Constant):**

- $PK_a$ – 12.62

**Flow ability:**

Crystalline sucrose is free flowing, whereas powdered sucrose is a cohesive solid.

**Melting Point:**

- 160 – 186$^o$ C (with decomposition)

**Moisture content:**

- Finely divided sucrose is hygroscopic and absorbs up to 1% water

**Applications:**

- It's used in large volume infusions.
- Sucrose syrups are also widely used as vehicles in oral liquid dosage forms to enhance stability (or) to increase viscosity.
- Sucrose has been used as a diluents in freeze- dried protein products.
- Sucrose syrups are used as tablet- coating agents at concentrations between 50% & 67% w/w with higher concentrations, partial inversion of sucrose which makes sugar coating difficult
- Sucrose is used in foods & confectionery & therapeutically in sugar pastes that are used to promote wound healing.

# Beta Cyclodextrins

## Synonym:

- B- Cyclodextrin beta- cycloamylose
- Beta- dextrin
- Beta dexum

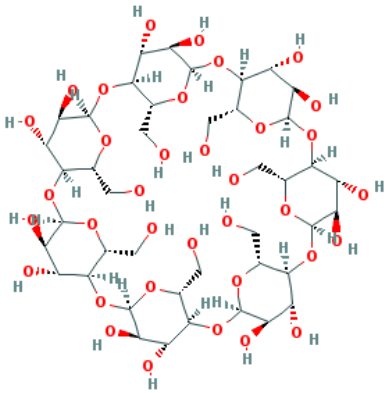
## Empirical Formula:

$C_{42}H_{7}0_{35}$

## Molecular Weight:

1135 g/Mol

## Structural Formula:



## Functional Category:

- Solubilizing agent
- Stabilizing agent

## Description:

Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

**Solubility:**

Soluble 1 in 200 parts of propylene glycol.

**Stability and storage conditions:**

It is stable in the solid state if protected from high humidity.It should be stored in a tightly sealed container , in a cool, dry place.

Handling precautions:

Should be handled in a well ventilated environment.

**Applications:**

- Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bio availability.
- Primarily used in tablet and capsule formation.
- Cholesterol free products.
- Bioavailability enhancer.

# CALCIUM CARBONATE

## Synonyms:

- Micro mite
- Pharma- Carb
- Precipitated Carbonate of line
- Precipitated chalk

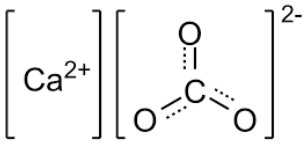
## Chemical Name:

Carbonic acid, calcium salt (1:1)

Empirical Formula and molecular weight:

$CaCO_3$ 100.09

## Structural Formula:




## Functional Category:

- Buffering agent
- Coating agent
- Opacifier
- Tablet and capsule diluents therapeutic agent

**Description:**

Calcium carbonate occurs as an odorless and tasteless white power (or) crystals

**Density: (bulk)**

0.8 g/cm$^3$

**Density: (tapped)**

1.2 g/cm$^3$

**Melting Point :**

Decomposes at 825$^o$C

**Solubility:**

Practically insoluble in ethanol (95%) and Water Solubility in water is increased by the presence of ammonium salts (or) carbon dioxide the presence of alkali hydroxides reduces solubility.

**Stability and storage conditions:**

Calcium carbonate is stable & should be stored in a well- closed container in a cool, dry place.

**Incompatibilities:**

Calcium carbonate is prepared by double decomposition of calcium chloride and sodium bi carbonate in aqueous solution. Density and fineness are governed by the concentrations of the solutions. Calcium carbonate is also obtained from the naturally occurring minerals, aragonite, calcites and vaterite.

**Safety:**

Calcium carbonate is mainly used in pharmaceutical formulations and is generally regarded as a non toxic material. Calcium carbonate administered orally may cause constipation and flatulence.

**Handling Precautions:**

Observe normal precautions appropriate to the circumstances & quantity of material handled. Calcium Carbonate may be irritant to the eyes and on inhalation. Eye protection, gloves, and a dust mask are recommended. Calcium carbonate should be handled in a well ventilated environment.

**Applications:**

- Calcium carbonate, employed as pharmaceutical excipient.
- Mainly used in solid dosage forms as a diluents.
- It's also used as base for medicated dental preparations, as a buffering agent and as a dissolution and in dispersible tablets.
- Calcium carbonate is used as a bulking agent in tablet sugar coating processes and as an pacifier in tablet film coating.
- Calcium carbonate is also used as a food additive and therapeutically as an antacid and calcium supplement.

# Glucose, Liquid

## Synonyms:

- Corn Syrup
- Floys
- Glucomalt
- Glucose Syrup
- Glucosweet
- My lose
- Starch syrup

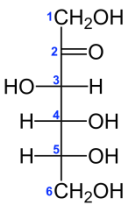
## Chemical Name:

Liquid glucose

## Empirical formula and Molecular weight:

$C_6H_{14}O_7$ 198.171 g/mol

## Structural Formula:




## Functional Category:

Coating agent, sweetening agent, tablet binder

## Molecular weight:

198.17116 g/mol

**Description:**

Liquid glucose is an aqueous solution of several compounds, principally dextrose, dextrin, fructose and maltose, with other oligo saccharin and polysaccharides. It's a colorless odorless, and viscous sweet tasting liquid, ranging in color from colorless to straw- colored.

**Density:**

Miscible with water, partially miscible with ethanol (90%)

**Stability and storage conditions:**

Liquid glucose should be stored in a well closed container in a cool, dry place. Elevated temperature will cause discoloration.

**Incompatibilities:**

Incompatible with strong oxidizing agents.

**Method of Manufacture:**

Liquid glucose is prepared by the incomplete acidic (or) enzymatic hydrolysis of starch.

**Safety:**

Liquid glucose is used in oral pharmaceutical formulations and confectionery products and is generally regarded as a nontoxic and non irritant material. It may be consumed by diabetics.

**Handling Precautions:**

Observe normal precautions appropriate to the circumstances and quantity of material handled.

**Applications in Pharmaceutical formulation:**

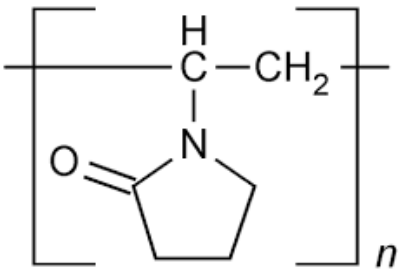
- Liquid glucose is used as a base in oral solution and syrups and also as a granulating and coating agent in tablet manufacture.
- In sugar solutions for tablet coating liquid glucose is used to retard the crystallization of the sucrose.
- Liquid glucose is also used in confectionery products.

# CROS POVIDONE

**Synonyms:**

Cross linked povidone poly vinyl poly pyrrolidone PVPP

**Structure:**




**Empirical Formula & Molecular Weight:**

$(C_6H_9No)$ n 1000-000

Crospovidone is a water insoluble synthetic cross linked homopolymer of N-vinyl- 2 – Pyrrolidone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

**Functional Category:**

Tablet Disintegrant

**Description:**

Crospovidone is a white to creamy- white, finely divided, free- flowing, practically tasteless, odorless (or) nearly, odorless, hygroscopic powder.

**Typical Properties:**

**Acidity/ alkalinity:**

$P^H$- 5.0-8.0 (1% w/v aqueous slurry)

**Density:**

1.22 g/cm$^3$

**Moisture Content:**

Maximum moisture sorption is approximately 60%

**Solubility:**

Practically insoluble in water & most common organic solvents.

**Stability & Storage conditions:**

Crospovidone is hygroscopic; it should be stored in an airtight container in a cool, dry place.

**Incompatibilities:**

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adduct with some materials.

**Method of Manufacture:**

Acetylene and formaldehyde are reacted in the presence of a highly active catalyst to form butynediol, which is hydrogenated to butanediol& then cyclodehydrogenated to form butyrolactone. Pyrrolidone is produced by reacting butyrolactone with ammonia. This is followed by a vinylation reacting in which pyrrolidone& acetylene are reacted under pressure. The monomer vinyl pyrrolidone is then polymerized in solution, using a catalyst. Crospovidone is prepared a Popcorn polymerization Process.

**Safety:**

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a non toxic & non irritant material.

**Handlings Precautions:**

Observe normal precautions appropriate to the circumstances and quanitity of material handled Eye protection & a dust mask are recommended.

**Applications:**

- Tablet disintegrate
- Dissolution agent
- It’s also used as a solubility enhancer.

# Glycerol

**Synonyms:**

- Concentrated glycerin
- Glycerolum

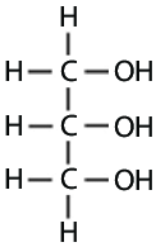
**Empirical Formula:**

$C_3H_8O_3$ 92.09

**Chemical Name:**

Propane -1, 2, 3 – triol (56-81-5)

**Structural Formula:**



**Functional Category:**

- Antimicrobial Preservative
- Emollient
- Humectants
- Plasticizer
- Solvent
- Sweetening agent
- Tonicity agent

**Applications:**

Glycerin is used in wide variety of pharmaceutical formulations including oral, otic, opthalmic, topical &Parentral preparations.

**Descriptions:**

Glycerin is a clear, colorless, odorless, viscous, hygroscopic liquid, it has a sweet taste.

**Solubility:**

Soluble in 95% ethanol, Slightly soluble in acetone, practically insoluble in.

| | | |
|---|---|---|
| Boiling point | : | 290$^{o}$C (with decomposition) |
| Density | : | 1.2656 9/cm$^{3}$ at 15$^{o}$C |
| | | 1.2636 9/cm$^{3}$ at 20$^{o}$C |
| Hygroscopicity | : | Hygroscopic |
| Melting Point | : | 17.8$^{o}$C |

Glycerin is hygroscopic. Pure glycerin is not prone to oxidation by the atmosphere under ordinary storage conditions but it decomposes on heating, with the evolution of toxic aerolein. Mixtures of glycerin with water, ethanol (95%), & Propylene glycol are chemically stable.

Glycerin may crystallize if stored at low temperature; the crystals do not melt until warmed to 20$^{o}$C.

Glycerin should be stored in an airtight container, in a cool, dry place.

**Incompatibilities:**

Glycerin may explode if mixed with strong oxidizing agents such as chromium trioxide, potassium chlorate (or) potassium permanganate.

**Safety:**

- Glycerin is used in a wide variety of pharmaceutical formulations including oral, opthalmic, parental, and topical preparations. Adverse effects are mainly due to the dehydrating properties of glycerin.
- Oral doses are demulcent and mildly laxative in action large doses may produce headache, thirst, nausea, and hyperglycemia.
- When used as an excipient (or) food additive, glycerin regarded as a non toxic&non irritant material.

**Handling precautions:**

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended Glycerin is combustible and may react explosively with strong oxidizing agents.

**Applications, in Pharmaceutical formulation:**

Glycerin is used in a wide variety of pharmaceutical formulations including oral, otic, opthalmic, topical, and parental preparations.

# CHAPTER X

# RESULTS AND DISCUSSION

# CHAPTER – X

# RESULTS AND DISCUSSION

## I. STANDARD CURVES FOR LYMECYCLINE

### a. Preparation of Calibration medium:

The calibration medium pH (6.8) were prepared by using phosphate buffer as per the IP procedure (I.P. 2014)

### b. Estimation of absorption maximum ($\lambda_{max}$):

The $\lambda_{max}$ of Lymecycline was estimated by scanning the 10µg/ml concentration of the drug solution in buffer solution of phosphate pH 6.8. It showed the $\lambda_{max}$ (Narendrachary, et al., 2012) in phosphate buffer solution of pH 6.8 and the results were tabulated **Figure 1**.

### c. Preparation of standard curves:

The standard curves of Lymecycline prepared by using phosphate buffer pH (6.8}. The linear correlation coefficient was found to be 0.999 for pH (6.8) Lymecycline obeys the Beer's law within the concentration range of 2 to 10µg/ml **Figure 2**.

## II. INFRARED (IR) SPECTROSCOPIC STUDIES:

Infrared (IR) spectroscopic studies were carried out to confirm the compatibility between drug and the polymers used for the preparation of the chewing gum. The IR studies were performed for pure drug polymers and physical mixture of drug with polymers. The spectra studies at 4000$cm^{-1}$ to 400$cm^{-1}$. The principal peaks for pure drug were observed at wave numbers 3290 $cm^{-1}$, 2108 $cm^{-1}$, 1334 $cm^{-1}$.

| S.No | Functional Groups | Range | Wave Numbers |
|---|---|---|---|
| 1. | N – H Stretching | 3300-3500 $cm^{-1}$ | 3290 $cm^{-1}$ |
| 2. | C ≡ C Stretching | 2140-2100 cm-1 | 2108 $cm^{-1}$ |
| 3. | C – N Stretching | 1360-1080 cm-1 | 1334 $cm^{-1}$ |

It was found from the spectra that there was no major shifting as well as any loss of functional peaks in the spectra of drug, polymers and physical mixture of drug with polymers. This clearly indicated that there was no interaction between the drug and the polymer and the drug was present in its unchanged form.

**III. DIFFERENTIAL SCANNING CALORIMETRIC STUDIES (DSC):**

Differential scanning calorimetric studies (DSC) are commonly used to find out the interactions between the drug and excipients. DSC thermograms of pure drug, polymers and its physical mixtures were shown in the table. When comparing the thermal behaviors of the pure drug, the physical mixture of drug in polymer, analysis of the DSC curves can predict any interactions. DSC thermo gram of pure drug (Lymecycline) showed a sharp endothermic peak at No shifts in the endothermic peak of Lymecycline was observed in the DSC thermo gram of physical mixture of Lymecycline and polymers Lymecycline which suggested clearly that there was no interaction between the drug & the polymers and thus the drug found to be existed in its unchanged form. (Clarks analysis of drugs and poisons, third edition.,&sathish M Havanoor.et al 2014) **Figure. 3A**.

## III. FORMULATION OF LYMECYCLINE CHEWING GUM:

The Lymecycline chewing gum was prepared by Melting method (KoppulaRajitha et al., 2016). The principles of this method was based on the melting of gum base in a china dish, to this add other ingredients and mixed well and rolled in $CaCO_3$ powder, where chewing gum is cut into required size and shape. Basic advantage of the melting technique was it is simple and had a low cost. Lymecycline chewing gum was prepared by following process:

- Formulation of Lymecycline chewing gums with polymer.
- Formulation of chewing gums with lymecycline pure gum.
- Melting of gum base to obtain the medicated chewing gums.

Various formulations of Lymecycline chewing gums (F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13, F14, F15, F16) or F1 to F16 were prepared by using different polymers like (PEG-4000, PVA, Cros povidone,β – CD)at different concentrations were used.

## IV. CHARACTERIZATION OF LYMECYCLINE CHEWING GUM

All the formulations were evaluated for its drug content, solubility studies, in vitro drug release studies.

### a. Determination of drug content:

The drug content of all chewing gum formulations (F1 to F16) was in the range of 90.82% to 98.03%. The results were shown in table. The results suggest that the process employed to prepare the chewing gum shown distribution of drug **(Figure 5)**.

**b. Solubility studies:**

Solubility studies of pure drug (Lymecycline) and selected formulation (F8) were shown in Table & figure. The best formulation (F8) Chewing gum formulations, shown highest solubility in distilled water as compared with pure drug.

- The solubility of formulations {F8} and pure drug in phosphate buffer pH (6.8) were 8.05g/10ml and 9.97g/10ml respectively. Thus the solubility of Lymecycline chewing gums was increased approximately by ten folds when compared to pure drug. Hence, the noticeable increased saturation solubility of Lymecycline in the formulation of chewing gums was mainly attributed to the decreased particle size & increased surface area. The results can be explained by the Ostwald-Freundlich equation which demonstrates that the saturation solubility of the drug increases with reduction of particle size (Dianruizhang et al., 2012)

**In vitro dissolution studies:**

The dissolution study was carried out in pH 6.8 for 30 minutes. The invitro dissolution studies of all formulations were compared with pure drug. The results of in vitro drug release studies from the Lymecycline chewing gums were shown in the & in when compared the In vitro release profile of all the formulations are significantly greater than that pure drug Lymecycline **Figure. 9A**.

Formulations [F1, F2, F3, F4] were prepared using different concentrations of polymer shown the percentage drug release of 85.13%, 82.69%, 79.78%, 75.43% at 30 minutes respectively **Figure. 9B**.

Formulations [F5,F6,F7,F8] were prepared using different concentrations of polymer shown the percentage drug release of 90.28%, 92.89%, 94.26%, 98.26% at 30 minutes respectively **Figure. 9C**.

Formulations [F9, F10, F11, F12] prepared using different concentrations of polymer shown the percentage drug release of 90.63%, 85.52%, 80.52%, 83.47% at 30 minutes respectively. Formulations [F9, F10, F11, F12] prepared using different concentrations of polymers shown the percentage drug release of 91.76%, 88.59%, 85.39%, 81.96% at 30 minutes respectively **Figure. 9D**.

The percentage drug release of all the formulations were found to be in the following order. The release rate of the drug from the chewing gums were increased, on increasing the polymers concentrations.

The increased percentage drug release of polymer [β-CD] having formulation (F8) indicates that, polymer was used for the chewing gum stabilization as this water soluble polymer offers adequate surface active properties and it indicates that they have increased the drug release (Amighi. K et al., 2005) The increased percentage drug release of polymer having formulation (F8) indicates that, polymer was used as water soluble compound, in order to improve the drug dissolution rate (Noushin Bolourchian et al., 2013).

**COMPARISON OF DISSOLUTION DATA OF LYMECYCLINE CHEWING GUM CONTAINING DIFFERENT POLYMERS:**

The chewing gums are prepared with different polymers showed maximum drug release of 98.26%whereas chewing gums containing β-cyclodextrins **Figure. 9A-9D**.

## SELECTION OF BEST FORMULATION

Among Sixteen formulations, the best was selected on the basis of rapid drug release profile, lesser moisture absorption ratio, stickiness is also absent. Formulation F8 showed faster drug release rate of 98.26% in 30 minutes, comparatively less moisture absorption ratio of 15%, Nil stickiness and stability is maintained during the study period. In these parameter would drive the F8 formulation as a best comparatively.

## EVALUATION OF BEST FORMULATION

### a. Differential scanning Calorimetric studies:

Any possible drug polymer interaction can be studies by thermal analysis. The DSC thermo gram of Lymecycline exhibited an endothermic peak at corresponding to its melting point. The thermogram of the final best formulation of Lymecycline with other excipients shows the existence of drug endothermic peak within the range which indicated the absence of interaction between the drug and other excipients. The DSC thermogram of pure drug and the final best formulation is presented in **Figure 19**.

### b. Fourier transforms infrared (FTIR) spectroscopic studies

Infrared spectra of the Lymecycline chewing gum showed major peak at indicated that there was no interaction between the drug and the final formulation throughout the preparation of medicated chewing gum. The result was shown in **Figure 3**.

| S.No | Functional Groups | Range | Wave Numbers |
|---|---|---|---|
| 1. | N – H Stretching | 3300-3500 $cm^{-1}$ | 3290 $cm^{-1}$ |
| 2. | C ≡ C Stretching | 2140-2100 cm-1 | 2108 $cm^{-1}$ |
| 3. | C – N Stretching | 1360-1080 cm-1 | 1334 $cm^{-1}$ |

**STABILITY STUDIES**

The formulation F8 was selected for stability studies on the basis of their high cumulative percentage drug release and also results of less moisture absorption ratio. The stability studies carried out at 25˚C (room temperature) & 40˚C/75˚ RH for the best formulations up to 30 days. In 15 day time interval, the chewing gums were analyzed for hardness, drug content uniformity, % drug release up to 30 days. The formulation showed not much variation in any parameter. The results shown in **Figure 17**. From these results, it was concluded that formulation F8 (β-cyclodextrin) was stable and retained its original properties. The results obtained are tabulated in **Table 12A**.

**POST COMPRESSION EVALUATION STUDIES**

**a. General appearance**

The formulated chewing gums were orange in color. All chewing gums were elegant in appearance **Table. 8**.

**b. Drug content of Lymecycline chewing gum**

The drug content of the best formulation as given (F8-βCD) in **Table.6** which shows an uniform drug content in the formulation.

**c. Thickness and Diameter**

The thickness for the best formulation was (F8-βCD). The result was summarized in Table and **Figures 6**. The diameter of the best formulation was (F8-βCD). The results indicated a uniform particle size distribution and no deformities.

**d. Hardness:**

The hardness for the best formulation was found to be (F8). The results indicated that the tablets of formulation have good hardness, which in turn protects from mechanical damage. The results were summarized in **Table 6**.

**e. Weight Variation:**

The average weight of the best formulation (F8) was found to be 1.010 ± 0.005 mg and tabulated in **Table 6**. The best formulation chewing gums passes weight variation test and the weight variation was within the pharmacopoeia limits of ± of the weight. The results indicated that all chewing gums of best formulation (F8-βCD) have uniform weight.

**f. Comparison of Invitro dissolution studies of Lymecycline chewing gum with Lymecycline pure drug:**

The dissolution study was carried out in pH 6.8. Invitro drug release profile of Lymecycline chewing gums (best formulation F8 – βCD) showed better dissolution rate (98.26%) when compared with marketed capsules [92.89%]. The results were shown in **Figure. 16**.

**g. Anti-Microbial activity of Prepared Medicated Chewing Gum**

The anti-microbial activity was carried out in organism streptococci & staphylococci and Amikacin was used as a standard drug. The results were shown in **Table. 13. Figure. 20.**

**TABLE: 1 CALIBRATION OF LYMECYCLINE BY USING PHOSPHATE BUFFER pH– 6.8**

| S.NO. | Concentration (µg/ml) | Absorbance ± SD |
|---|---|---|
| 1. | 5 | 0.1421 ± 0.010 |
| 2. | 10 | 0.2901±0.016 |
| 3. | 15 | 0.4289±0.022 |
| 4. | 20 | 0.5712±0.051 |
| 5. | 25 | 0.7003±0.048 |
| 6. | 30 | 0.8101±0.053 |

Regression Value = 0.99978 ± .001

## TABLE: 2 A TYPICAL GUM BASE FORMULA

| Ingredient | Amount (%) |
|---|---|
| Gum base | 20-90% |
| Softeners | 5-35% |
| Elastomers | 10% |
| Sweeteners | 30-60% |
| Texture agent/ filler | 4-50% |
| Colorants | Up to 1% |
| Flavoring agents | 2-5% |
| Humectants | 10% |
| Miscellaneous<br>(Preservatives, Antioxidants) | 0.1% |

## TABLE:3 COMPOSITION OF TYPICAL GUM BASE

| Components | Function |
|---|---|
| Elastomers and Poly vinyl acetate | Chewable synthetic material |
| Resins | Plasticizing agent |
| Waxes and fats | Softening/emulsifying agent |
| BHT | Anti-oxidant |

**TABLE: 4 FORMULATION OF MEDICATED CHEWING GUM BY MELTING METHOD (F1 TO F8)**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Lymecycline | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| Gum base | 200 | 200 | 200 | 200 | 250 | 250 | 250 | 250 |
| Glycerol | 10 | 15 | 20 | 25 | 10 | 15 | 20 | 25 |
| Sucrose | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Calcium Carbonate | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| Liquid glucose | 45 | 45 | 45 | 45 | 45 | 45 | 45 | 45 |
| Mannitol | 202 | 197 | 192 | 187 | 152 | 147 | 142 | 137 |
| Aspartame | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Flavor | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

Total weight of each chewing gum = 1000mg

**TABLE: 5 FORMULATION OF MEDICATED CHEWING GUM BY MELTING METHOD (F9 TO F16)**

| Ingredients | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 |
|---|---|---|---|---|---|---|---|---|
| Lymecycline | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| Gum base | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |
| Glycerol | 10 | 15 | 20 | 25 | 10 | 15 | 20 | 25 |
| Sucrose | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Calcium Carbonate | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| Liquid glucose | 45 | 45 | 45 | 45 | 45 | 45 | 45 | 45 |
| Mannitol | 102 | 97 | 92 | 87 | 52 | 47 | 42 | 37 |
| Aspartame | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Flavor | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

Total weight of each chewing gum: 1000mg

## TABLE: 6 POST COMPRESSION STUDY FOR LYMECYCLINE MEDICATED CHEWING GUM FORMULATIONS

| Formulation Code | Weight uniformity test ± SD | Drug content in percentage ± SD | Hardness ($kg/cm^2$) | Thickness (mm) ± SD | Friability ± SD |
|---|---|---|---|---|---|
| F1 | 996.9±.1.33 | 90.82±0.63 | 2.2±0.2 | 4.0±0.06 | 0.74±0.07 |
| F2 | 997.5±0.08 | 93.33±0.62 | 2.3±0.11 | 4.0±0.10 | 0.63±0.04 |
| F3 | 996.9±0.75 | 95.58±0.76 | 2.3±0.15 | 3.9±0.01 | 0.65±0.01 |
| F4 | 996.7±0.44 | 94.49±0.89 | 2.4±0.20 | 3.7±0.03 | 0.61±0.01 |
| F5 | 997.2±0.18 | 92.87±0.21 | 2.4±0.15 | 3.8±0.03 | 0.62±0.04 |
| F6 | 996.6±0.79 | 96.62±0.28 | 2.2±0.06 | 3.8±0.03 | 0.65±0.04 |
| F7 | 997.1±1.30 | 94.93±0.67 | 2.1±0.06 | 3.8±0.02 | 0.82±0.01 |
| F8 | 996.7±0.19 | 98.03±0.65 | 2.0±0.06 | 3.9±0.03 | 0.89±0.01 |
| F9 | 996.3±0.22 | 95.01±1.11 | 2.0±0.10 | 3.9±0.02 | 0.74±0.02 |
| F10 | 996.6±0.17 | 94.61±0.24 | 1.9±0.10 | 3.6±0.04 | 0.84±0.02 |
| F11 | 996.8±0.49 | 95.10±0.12 | 1.9±0.06 | 3.6±0.04 | 0.54±0.02 |
| F12 | 996.6±0.21 | 93.67±0.77 | 2.5±0.23 | 3.5±0.02 | 0.57±0.03 |
| F13 | 997.1±0.10 | 94.45±0.12 | 2.5±0.06 | 4.0±0.01 | 0.56±0.03 |
| F14 | 996.9±0.41 | 93.50±0.60 | 2.5±0.06 | 4.0±0.07 | 0.58±0.04 |
| F15 | 997.5±0.12 | 94.84±0.04 | 2.4±0.06 | 4.0±0.06 | 0.63±0.04 |
| F16 | 996.5±0.59 | 94.50±0.21 | **2.3**±0.06 | 4.0±0.02 | 0.68±0.15 |

**TABLE: 7 RESULTS OF WEIGHT VARIATION (%/wt)**

| No. | FORMULATIONS | WEIGHT VARIATIONS[g] |
|---|---|---|
| 1. | F1 | 1.080±0.05 |
| 2. | F2 | 0.995±0.06 |
| 3. | F3 | 1.012±0.06 |
| 4. | F4 | 1.086±0.06 |
| 5. | F5 | 1.290±0.05 |
| 6. | F6 | 0.981±0.01 |
| 7. | F7 | 1.016±0.03 |
| 8. | F8 | 1.010±0.05 |
| 9. | F9 | 1.003±0.01 |
| 10. | F10 | 1.008±0.05 |
| 11. | F11 | 1.016±0.08 |
| 12. | F12 | 1.051±0.01 |
| 13. | F13 | 1.014±0.06 |
| 14. | F14 | 0.999±0.04 |
| 15. | F15 | 1.005±0.01 |
| 16. | F16 | 1.072±0.03 |

**TABLE: 8 EVALUATION PARAMETERS OF MEDICATED CHEWING GUMS**

| S.NO. | FORMULATION CODE | COLOR | TEXTURE FEEL (OR) APPEARANCE | STICKINESS | DRUG CONTENT (%) |
|---|---|---|---|---|---|
| 1. | F1 | Light Orange | Good | NIL | 90.82±0.63 |
| 2. | F2 | Light Orange | Good | NIL | 93.33±0.62 |
| 3. | F3 | Light Orange | Hard | NIL | 95.58±0.76 |
| 4. | F4 | Light Orange | Good | NIL | 94.49±0.89 |
| 5. | F5 | Light Orange | Soft | NIL | 92.87±0.21 |
| 6. | F6 | Light Orange | Good | NIL | 96.62±0.28 |
| 7. | F7 | Light Orange | Good | NIL | 94.93±0.67 |
| 8. | F8 | Light Orange | Soft | NIL | 98.03±0.65 |
| 9. | F9 | Light Orange | Hard | NIL | 95.01±1.11 |
| 10. | F10 | Light Orange | Solid mass | NIL | 94.61±0.24 |
| 11. | F11 | Light Orange | Soft | NIL | 95.10±0.12 |
| 12. | F12 | Light Orange | Good | NIL | 93.67±0.77 |
| 13. | F13 | Light Orange | Good | NIL | 94.45±0.12 |
| 14. | F14 | Light Orange | Good | NIL | 93.50±0.60 |
| 15. | F15 | Light Orange | Soft | NIL | 94.84±0.04 |
| 16. | F16 | Light Orange | Soft | NIL | 94.50±0.21 |

±

## TABLE: 9 DETAILS OF DISSOLUTION STUDY

### DISSOLUTION TEST APPARATUS:

| | | |
|---|---|---|
| 1. | Speed | 50 strokes per min |
| 2. | Volume of Medium | 500 ml |
| 3. | Sample withdrawal at each time interval | 2.8 ml |
| 4. | Medium used | Phosphate buffer (pH 6.8) |
| 5. | Temperature | 37 ± 0.5˚ C |

## TABLE: 10A IN-VITRO RELEASE PROFILE OF MEDICATED CHEWING GUM LYMECYCLINE [F1-F8]

| FORMULATION CODE | 5TH MINUTE | 10TH MINUTE | 15TH MINUTE | 20TH MINUTE | 25TH MINUTE | 30TH MINUTE |
|---|---|---|---|---|---|---|
| F1-PVA | 47.7±0.82 | 55.5±1.05 | 62.67±0.81 | 69.90±1.04 | 75.43±0.84 | 85.13±0.69 |
| F2-PVA | 42.61±0.58 | 49.77±0.88 | 53.35±0.65 | 61.54±1.33 | 76.44±1.10 | 82.69±1.02 |
| F3-PVA | 42.83±0.70 | 58.35±0.65 | 66.95±2.53 | 71.93±2.86 | 75.06±1.22 | 79.79±0.83 |
| F4-PVA | 43.43±0.71 | 51.28±0.77 | 60.40±0.69 | 64.36±1.06 | 70.13±0.57 | 75.43±1.05 |
| F5-BCD | 55.43±1.03 | 63.13±0.91 | 70.77±1.43 | 75.44±1.13 | 84.34±1.57 | 90.28±0.99 |
| F6-BCD | 55.32±1.43 | 63.21±0.91 | 71.09±0.49 | 79.84±1.48 | 88.52±1.29 | 92.89±1.31 |
| F7-BCD | 55.54±0.87 | 64.89±2.15 | 73.05±1.26 | 73.45±0.23 | 89.27±0.23 | 94.26±0.56 |
| F8-BCD | 47.23±0.77 | 54.03±2.23 | 64.11±0.98 | 73.88±0.45 | 84.29±1.72 | 98.26±0.78 |

**TABLE: 10B IN-VITRO RELEASE PROFILE OF MEDICATED CHEWING GUM LYMECYCLINE**

| FORMULATION CODE | $5^{TH}$ MINUTE | $10^{TH}$ MINUTE | $15^{TH}$ MINUTE | $20^{TH}$ MINUTE | $25^{TH}$ MINUTE | $30^{TH}$ MINUTE |
|---|---|---|---|---|---|---|
| F9-PEG | 58.68±0.65 | 65.02±0.70 | 71.63±0.66 | 76.13±1.36 | 83.15±1.69 | 90.63±1.43 |
| F10-PEG | 47.69±0.81 | 55.52±1.05 | 62.67±0.81 | 68.90±1.04 | 76.46±0.96 | 85.49±0.73 |
| F11-PEG | 42.14±0.89 | 48.91±0.12 | 55.91±0.55 | 64.35±0.61 | 76.21±1.72 | 80.52±0.78 |
| F12-PEG | 31.63±0.69 | 38.73±1.18 | 45.72±1.08 | 56.72±1.08 | 66.01±1.50 | 83.47±1.66 |
| F13-CP | 45.22±1.91 | 56.46±1.67 | 67.51±0.45 | 76.36±0.24 | 81.93±0.76 | 91.76±0.56 |
| F14-CP | 42.61±0.93 | 60.89±2.12 | 68.27±0.92 | 76.19±1.87 | 81.81±1.94 | 88.59±1.09 |
| F15-CP | 50.43±0.55 | 63.68±0.86 | 69.10±0.96 | 74.59±1.06 | 79.75±0.39 | 85.39±0.39 |
| F16-CP | 40.79±1.48 | 49.12±2.59 | 55.5±1.03 | 64.19±0.48 | 77±0.55 | 81.96±0.81 |

## TABLE: 11 IN-VITRO RELEASE KINETICS DATA OF LYMECYCLINE CHEWING GUM

| Formulation Code | ZERO ORDER | | FIRST ORDER | | HIGUCHI | | KORSMEYER PEPPAS | | HIXSON CROWELL | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $r^2$ | $K^0(h^{-1})$ | $r^2$ | $K_1(h^{-1})$ | $r^2$ | $K_H(h^{-1/2})$ | $r^2$ | n | $r^2$ | $K_{HC}(h^{-1/3})$ |
| F1 | 0.813 | 2.611 | 0.945 | -0.034 | 0.970 | 16.39 | 0.968 | 1.491 | 0.853 | -0.072 |
| F2 | 0.823 | 2.723 | 0.969 | -0.044 | 0.975 | 17.03 | 0.956 | 1.491 | 0.922 | -0.083 |
| F3 | 0.798 | 2.746 | 0.986 | -0.048 | 0.969 | 17.39 | 0.988 | 1.520 | 0.939 | -0.086 |
| F4 | 0.902 | 2.703 | 0.967 | -0.034 | 0.992 | 16.29 | 0.968 | 1.304 | 0.929 | -0.075 |
| F5 | 0.864 | 2.805 | 0.985 | -0.041 | 0.990 | 17.26 | 0.974 | 1.383 | 0.952 | -0.083 |
| F6 | 0.853 | 2.816 | 0.968 | -0.084 | 0.983 | 17.38 | 0.957 | 1.436 | 0.918 | -0.091 |
| F7 | 0.794 | 1.821 | 0.995 | -0.010 | 0.967 | 11.55 | 0.991 | 1.351 | 0.994 | -0.029 |
| F8 | 0.817 | 1.970 | 0.989 | -0.012 | 0.973 | 12.36 | 0.973 | 1.350 | 0.965 | -0.034 |
| F9 | 0.796 | 2.016 | 0.983 | -0.013 | 0.964 | 12.76 | 0.976 | 1.401 | 0.970 | -0.035 |
| F10 | 0.829 | 1.904 | 0.998 | -0.012 | 0.981 | 11.91 | 0.995 | 1.301 | 0.998 | -0.032 |
| F11 | 0.796 | 1.946 | 0.998 | -0.012 | 0.966 | 12.33 | 0.983 | 1.381 | 0.991 | -0.034 |
| F12 | 0.794 | 2.036 | 0.987 | -0.013 | 0.964 | 12.89 | 0.975 | 1.412 | 0.982 | -0.036 |
| F13 | 0.800 | 2.719 | 0.989 | -0.043 | 0.971 | 17.22 | 0.992 | 1.509 | 0.951 | -0.081 |
| F14 | 0.796 | 2.734 | 0.990 | -0.045 | 0.968 | 17.34 | 0.983 | 1.516 | 0.955 | -0.083 |
| F15 | 0.760 | 2.673 | 0.947 | -0.053 | 0.950 | 17.17 | 0.980 | 1.584 | 0.858 | -0.087 |
| F16 | 0.827 | 2.654 | 0.939 | -0.039 | 0.969 | 16.51 | 0.925 | 1.481 | 0.890 | -0.077 |

**TABLE: 12A STABILITY STUDIES OF BEST FORMULATION [F8]**

| TEMPERATURE | DAYS | DRUG CONTENT (%) | HARDNESS ($kg/cm^2$) | DRUG RELEASE (%) |
|---|---|---|---|---|
| 25˚C | 15 | 98.00 ± 0.13 | 2.63 | 98.2% |
| | 30 | 97.8 ± 0.19 | 2.63 | 98.10% |
| 40˚C/75% RH | 15 | 97.9 ± 0.29 | 2.7 | 97.56% |
| | 30 | 97.6 ± 0.26 | 2.7 | 97.18% |

## TABLE: 12B IN VITRO DRUG RELEASE OF STABILITY STUDIES FOR THE BEST FORMULATION (F8)

| TIME IN MINUTES | CONTROL | 25˚C (ROOM TEMPERATURE) | | 40˚ / 75% RH | |
|---|---|---|---|---|---|
| | | 15TH DAY | 30TH DAY | 15TH DAY | 30TH DAY |
| 5 | 60.90±0.52 | 61.23±1.80 | 63.16±1.15 | 61.5±1.87 | 61.5±1.87 |
| 10 | 69.74±2.26 | 69.90±1.80 | 72.37±1.86 | 68.67±2.13 | 69.30±2.32 |
| 15 | 77.03±1.88 | 77±0.90 | 77.70±1.04 | 76.03±3.52 | 76.3±1.78 |
| 20 | 85.52±2.26 | 83.17±2.27 | 83.60±2.05 | 82.90±3.83 | 83.97±0.58 |
| 25 | 92.21±2.38 | 90.00±2.3 | 90.01±1.09 | 91.03±0.97 | 91.67±0.38 |
| 30 | 98.60±0.91 | 98.2±0.66 | 98.07±0.67 | 97.5±0.57 | 97.17±0.49 |

## TABLE: 13 ANTI – MICROBIAL ACTIVITY OF MEDICATED CHEWING GUM

| Sample Code (Lymecycline) | Streptococci | Staphylococci |
|---|---|---|
| Lymecycline | 15 mm | 14 mm |
| Standard drug (Amikacin) | 20 mm | 20 mm |

**FIGURE: 1 DETERMINATION OF λmax OF LYMECYCLINE IN PHOSPHATE BUFFER pH 6.8**

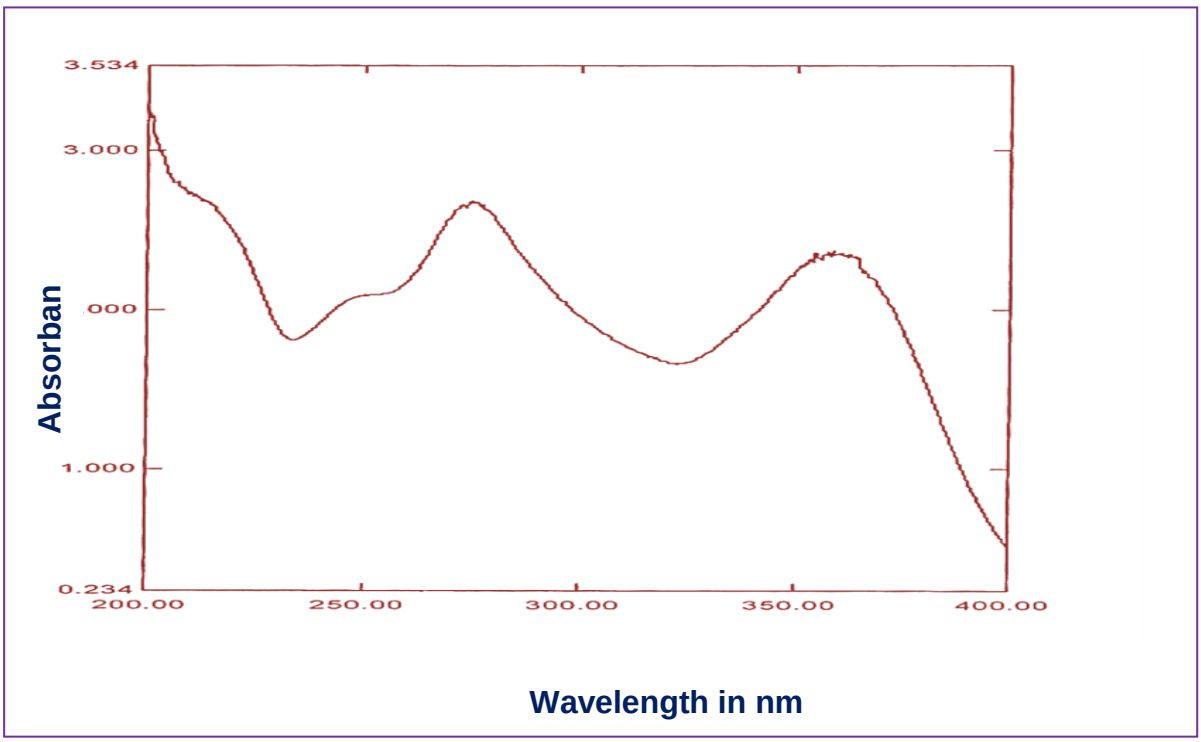



**FIGURE:2 CALIBRATION OF LYMECYCLINE BY USING PHOSPHATE BUFFER (PH 6.8)**

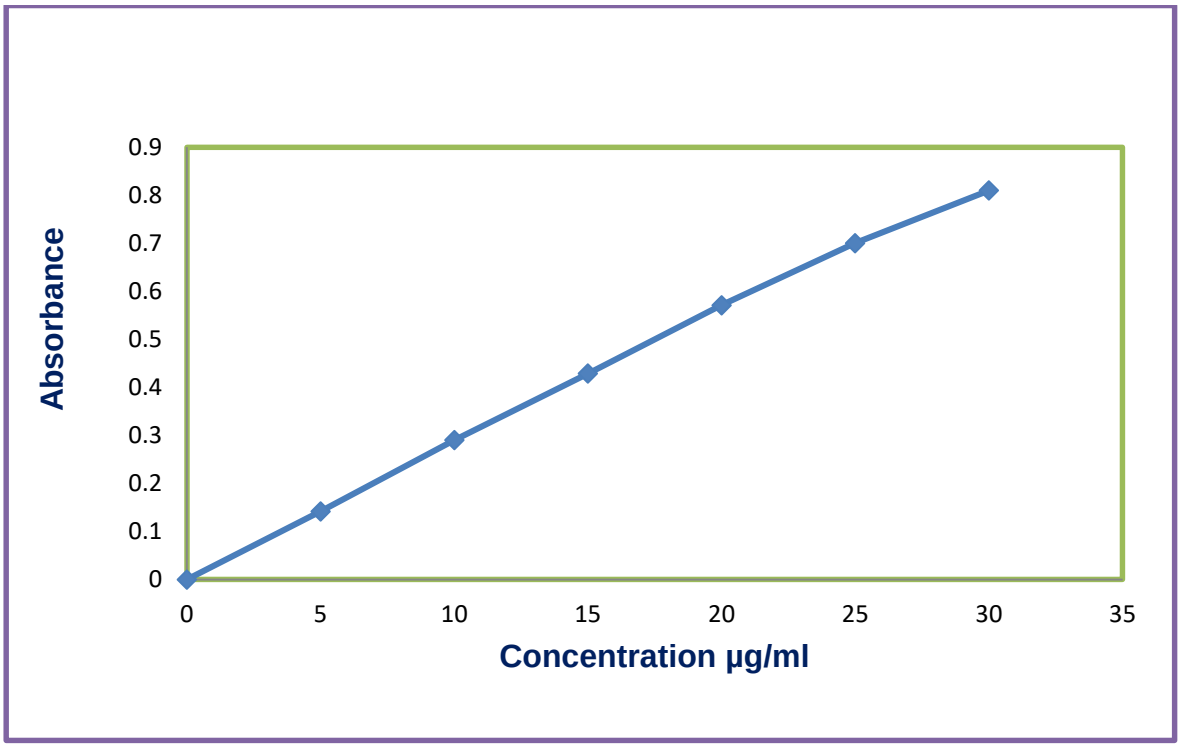


**FIGURE: 3A FT-IR SPECTRUM OF LYMECYCLINE**

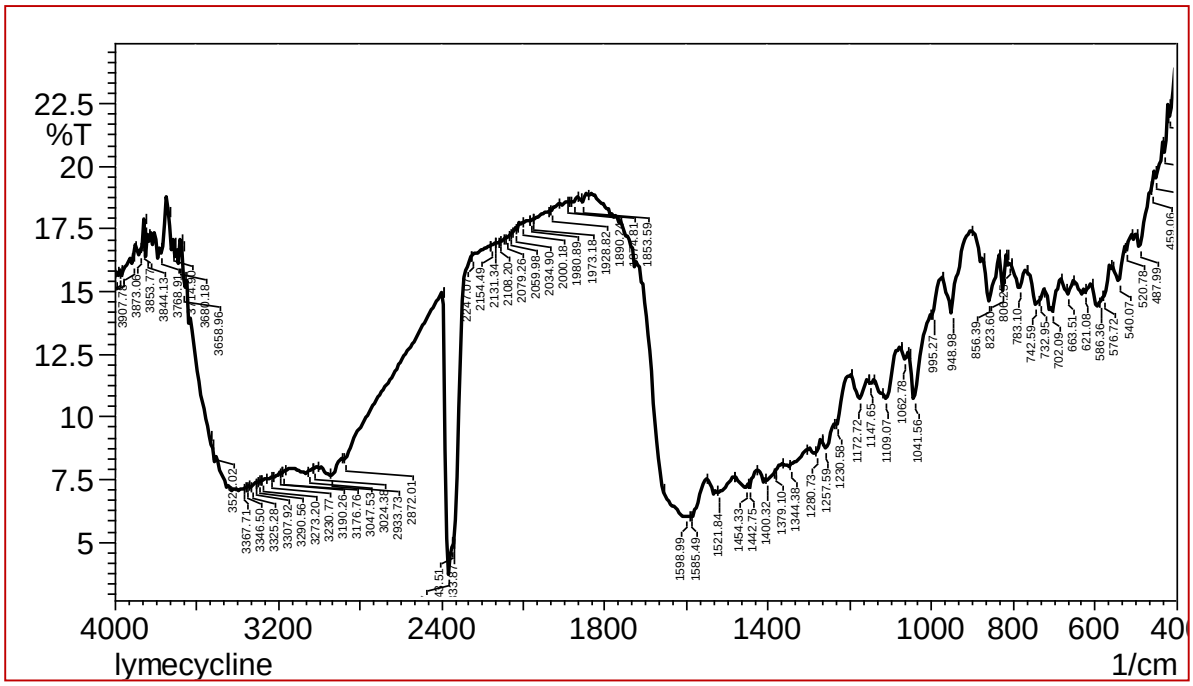



**FIGURE: 3B FT-IR SPECTRUM OF POLY VINYL ALCOHOL**

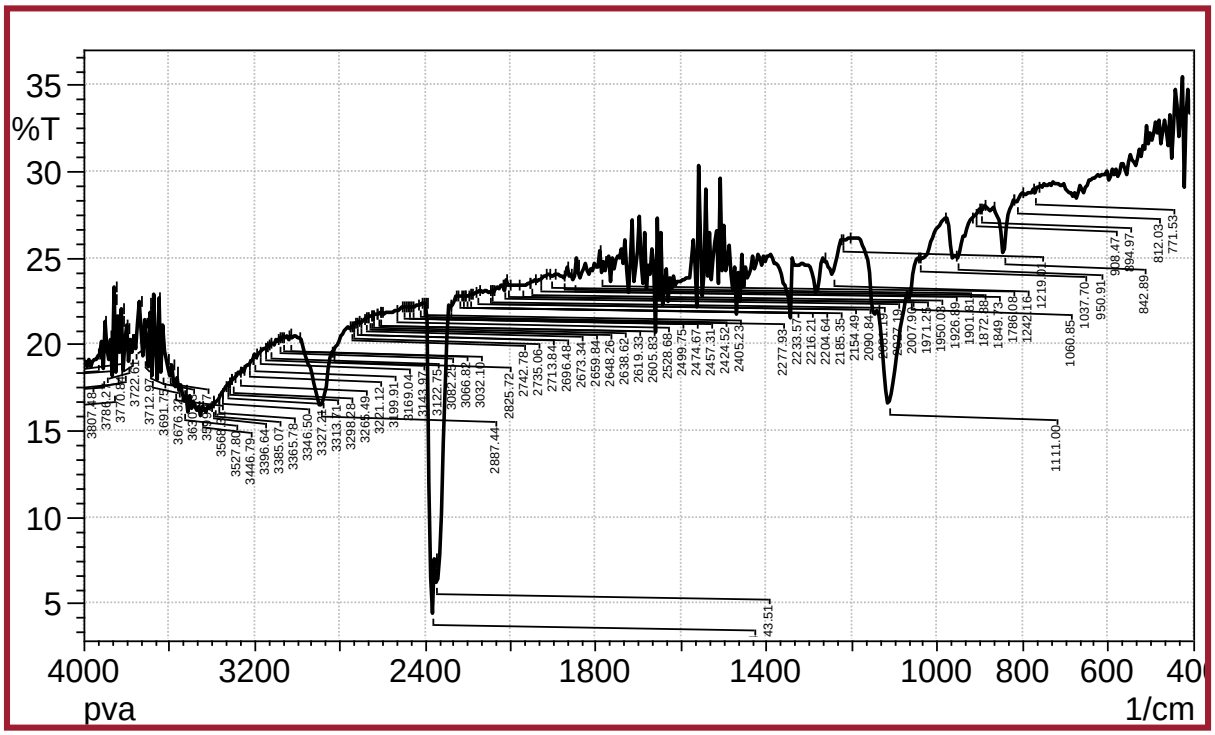


**FIGURE: 3C FT-IR SPECTRUM OF BETA CYCLODEXTRIN**

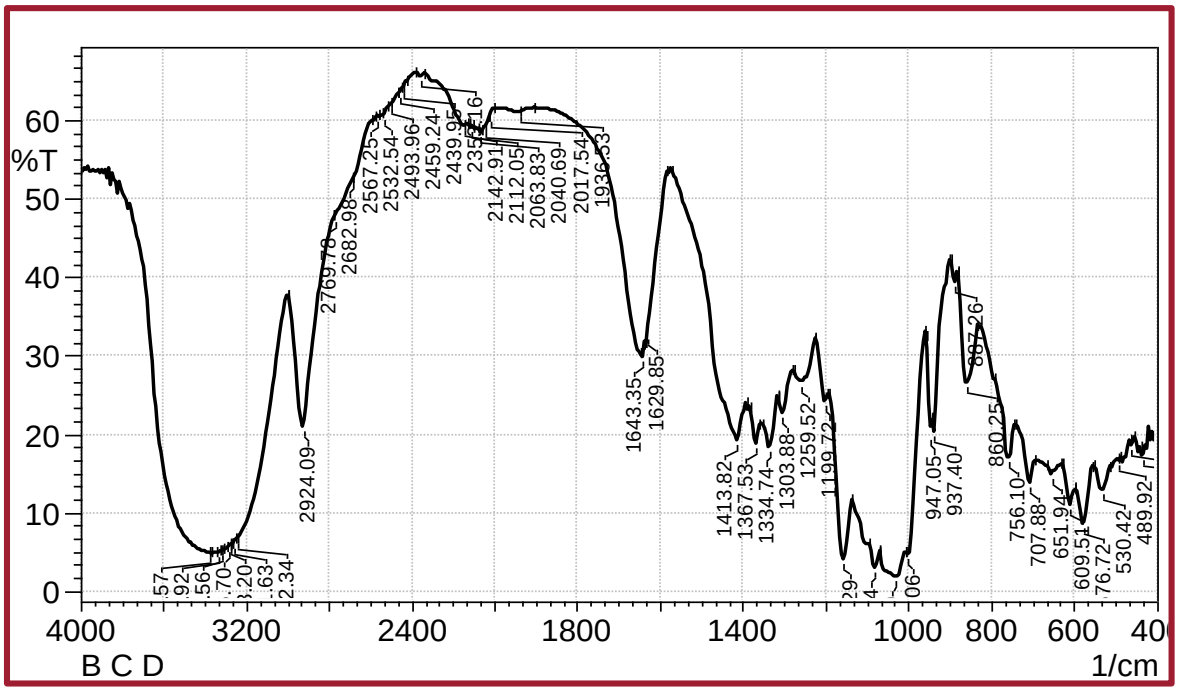



**FIGURE: 3D FT-IR SPECTRUM OF CROS POVIDONE**

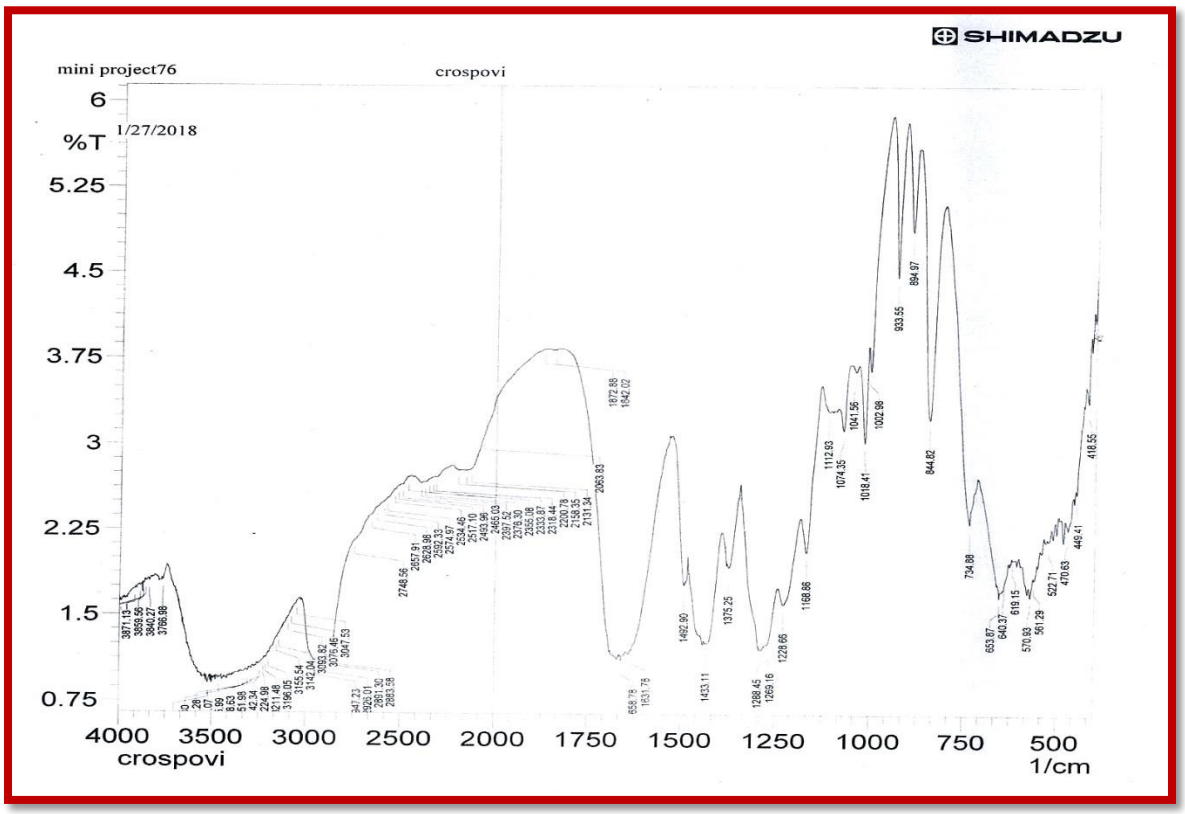


**FIGURE: 3E FT-IR SPECTRUM OF MANNITOL**

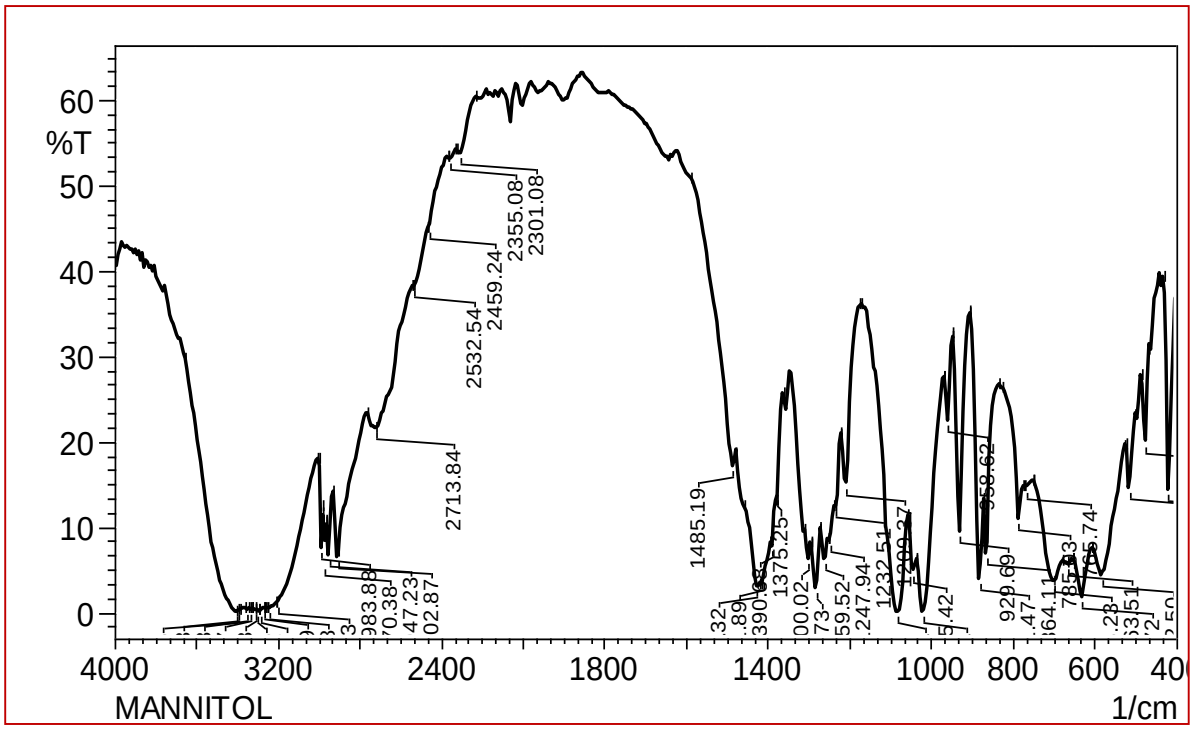



**FIGURE:3F FT-IR SPECTRUM OF CALCIUM CARBONATE**

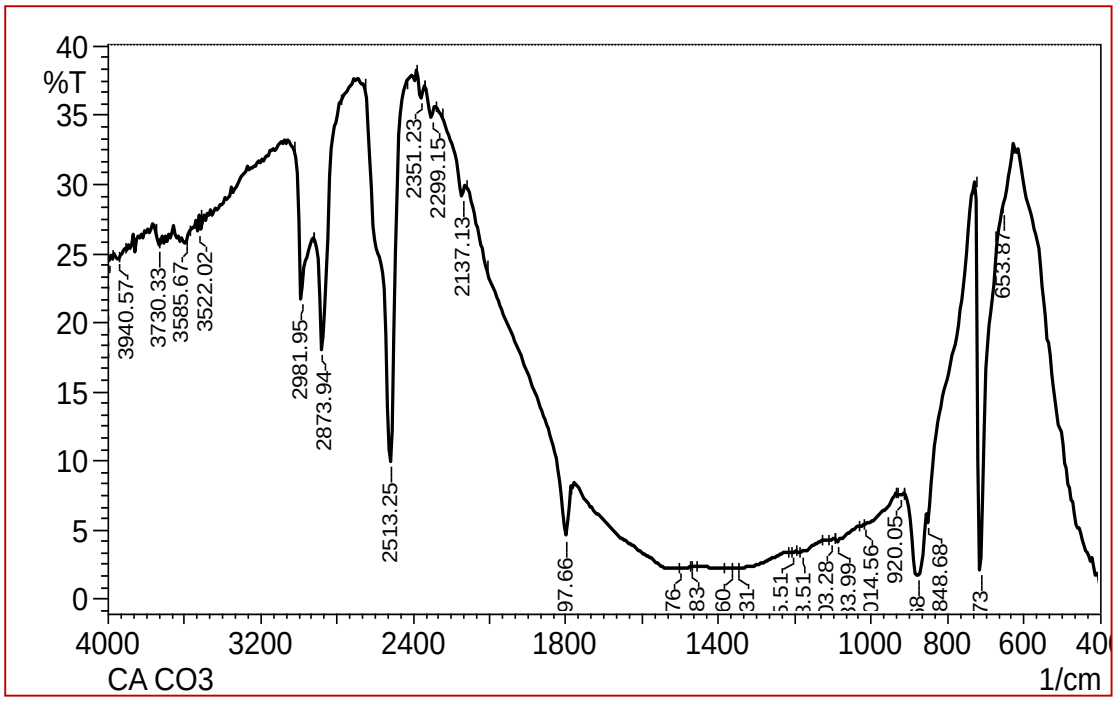


**FIGURE: 3G FT-IR SPECTRUM F LYMECYCLINE +PEG 4000**

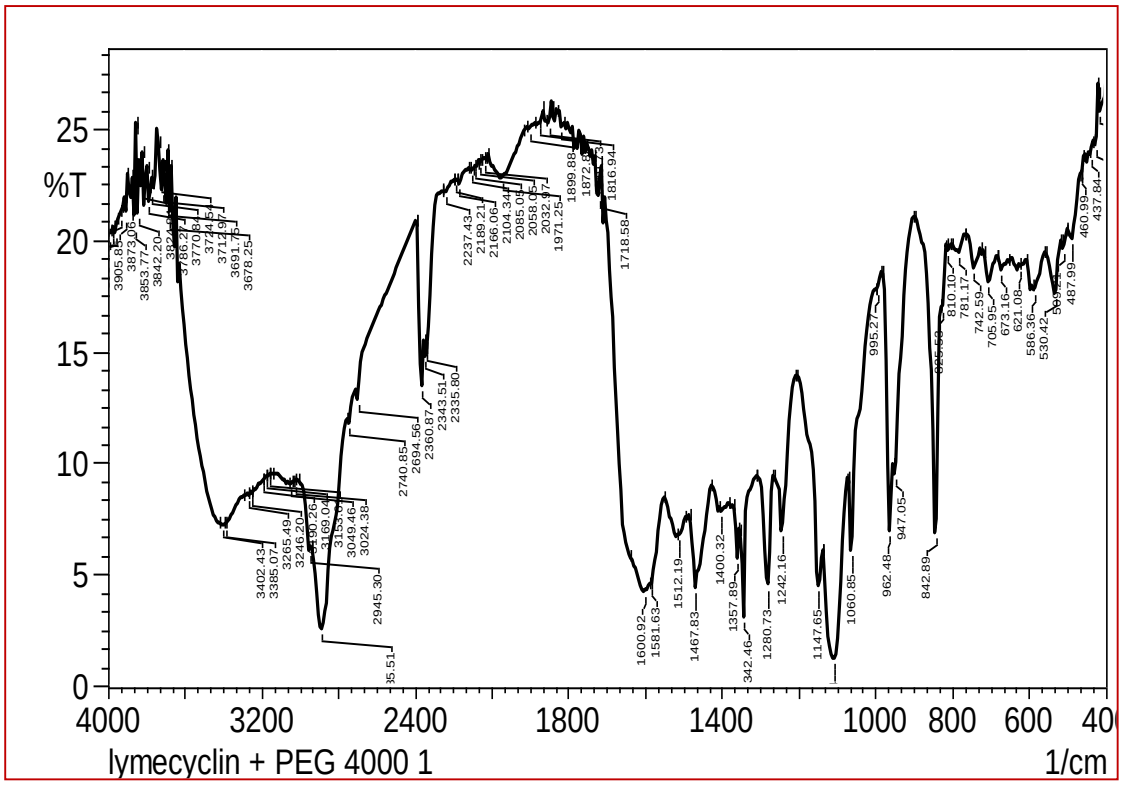



**FIGURE: 3H FT-IR SPECTRUM F LYMECYCLINE + CROSPOVIDONE**

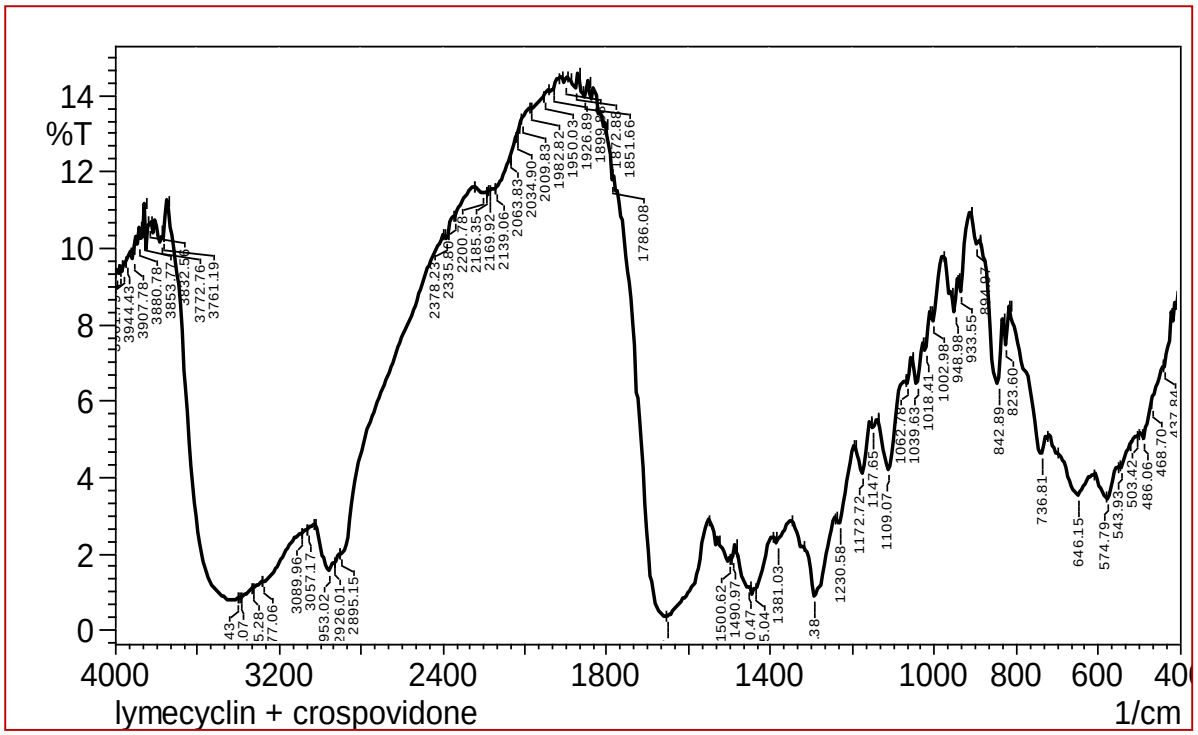


**FIGURE:3I FT-IR SPECTRUM F LYMECYCLINE + B-CD**

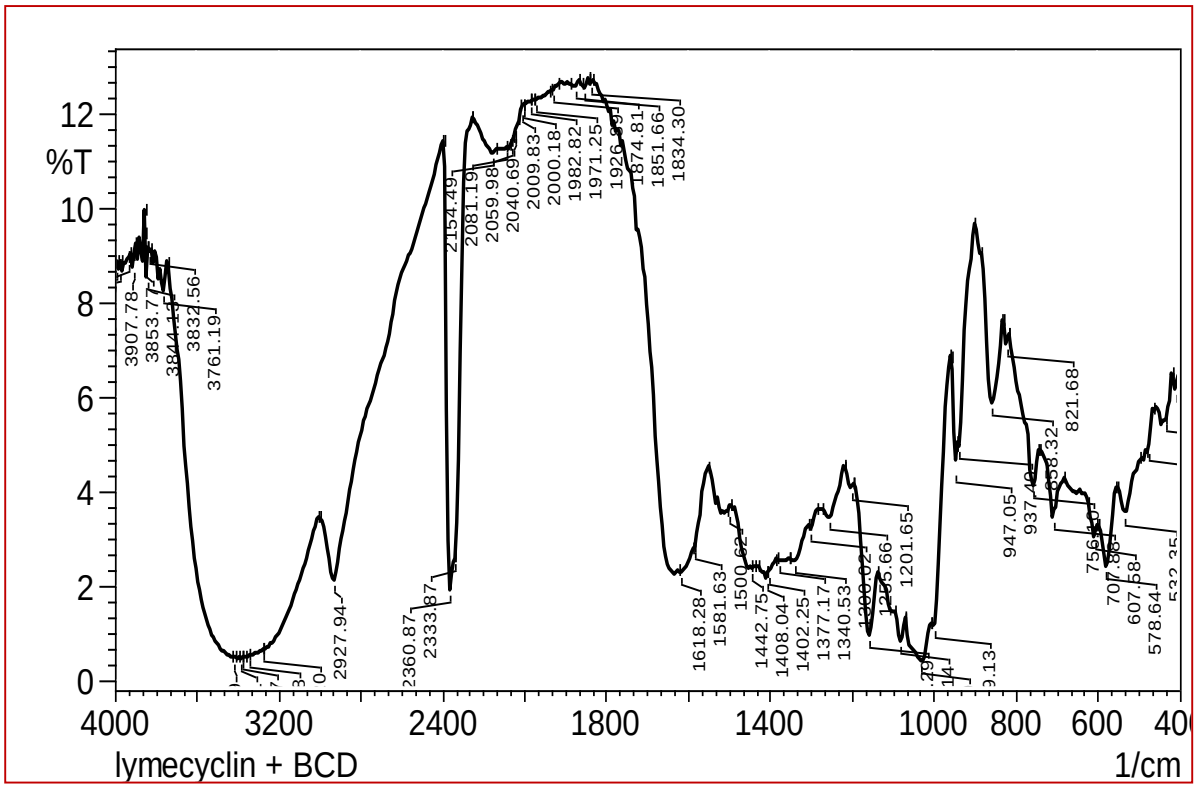



**FIGURE: 3J FT-IR SPECTRUM F LYMECYCLINE + PVA**

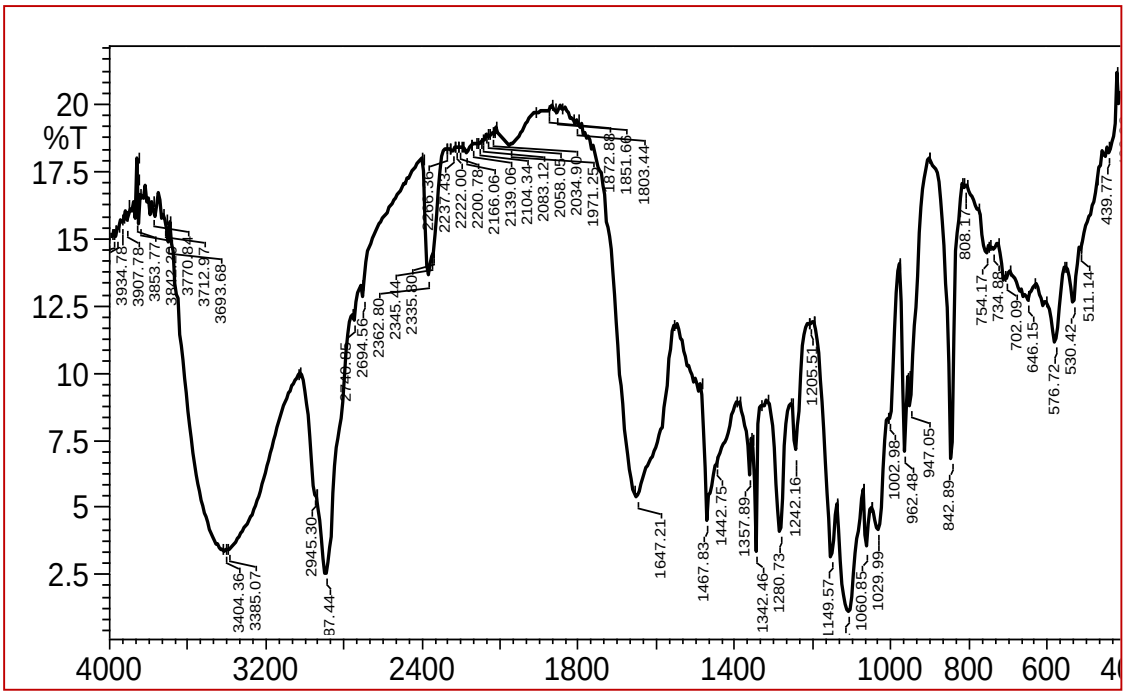


**FIGURE: 4 WEIGHT UNIFORMITY OF LYMECYCLINE MEDICATED CHEWING GUM**

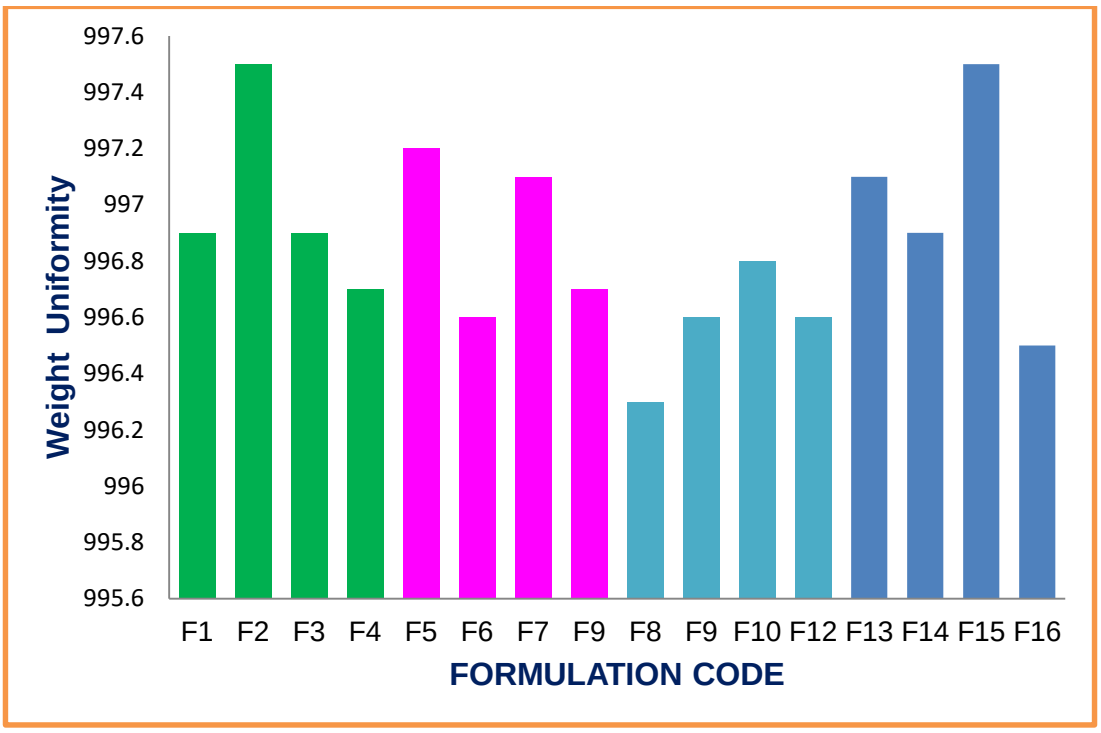



**FIGURE: 5 DRUG CONTENT FOR LYMECYCLINE MEDICATED CHEWING GUM**

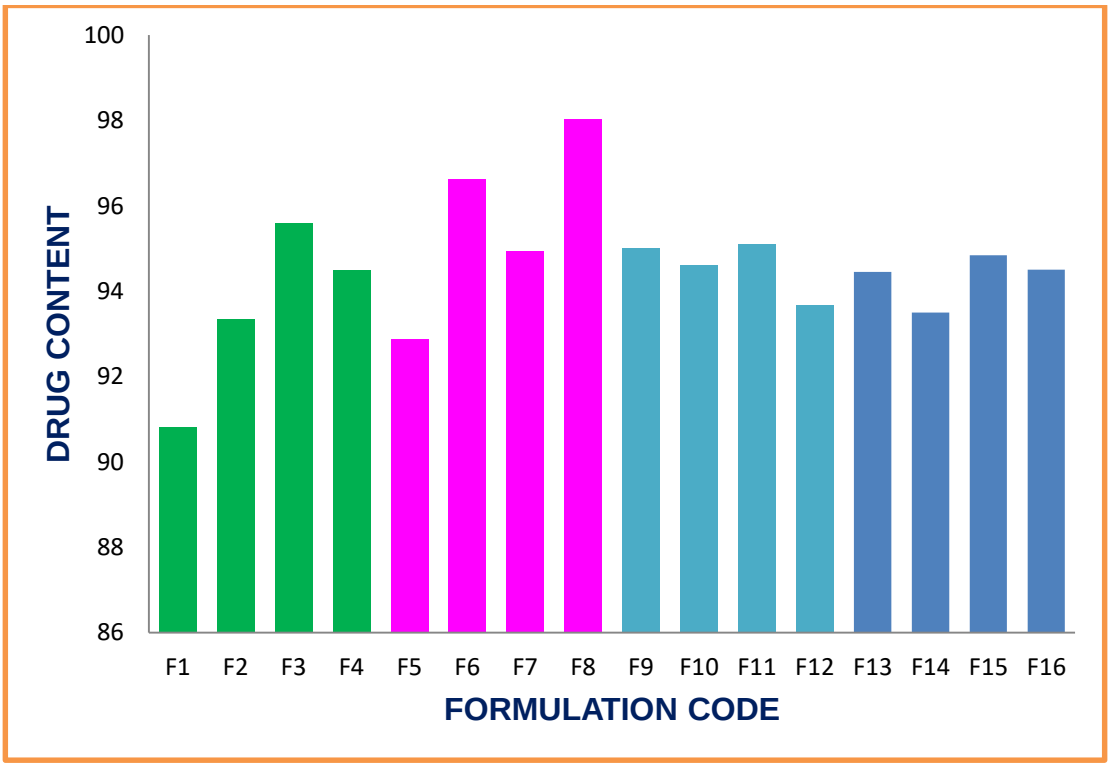


FIGURE: 6 HARDNESS OF LYMECYCLINE MEDICATED CHEWING GUM

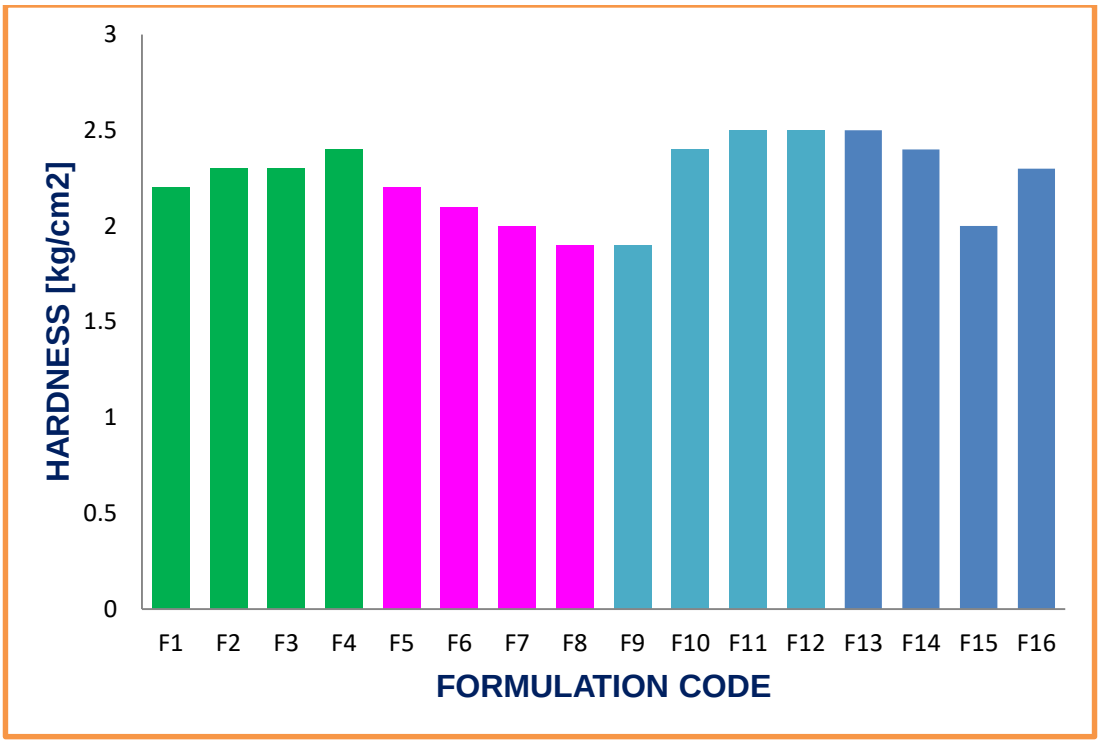



FIGURE: 7 THICKNESS OF LYMECYCLINE MEDICATED CHEWING GUM

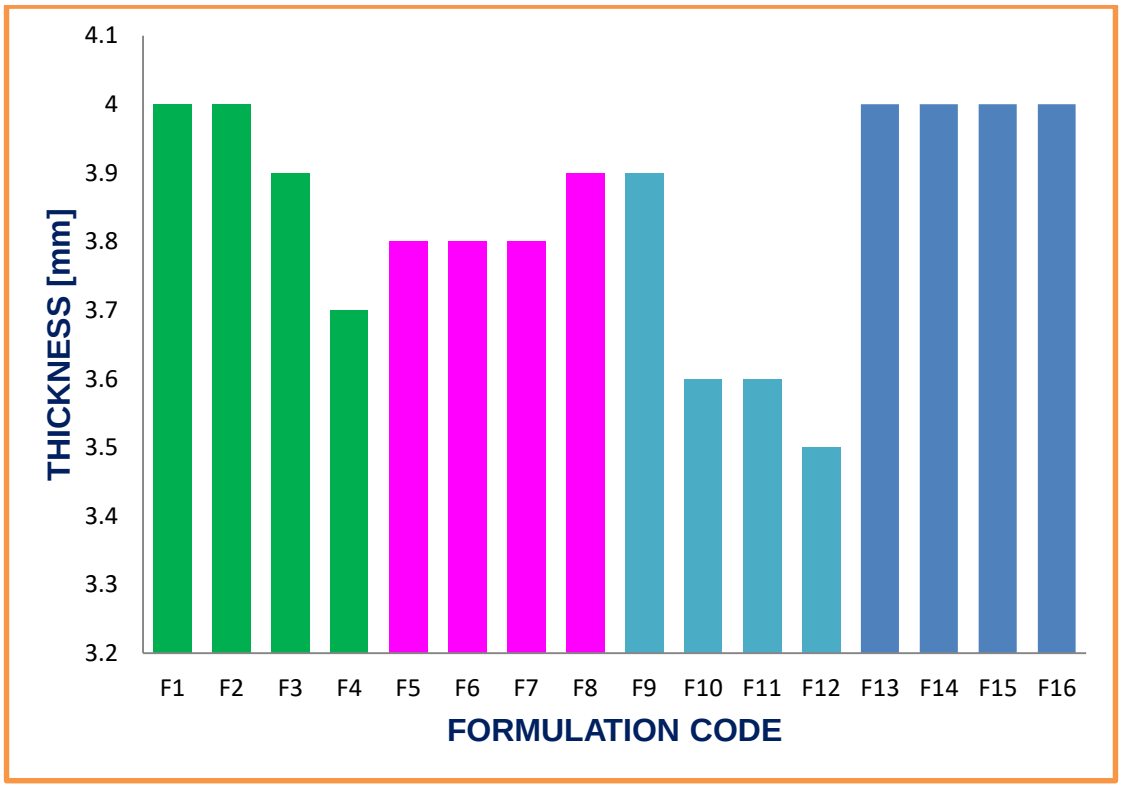


**FIGURE: 8 FRIABILITY FOR LYMECYCLINE MEDICATED CHEWING GUM**

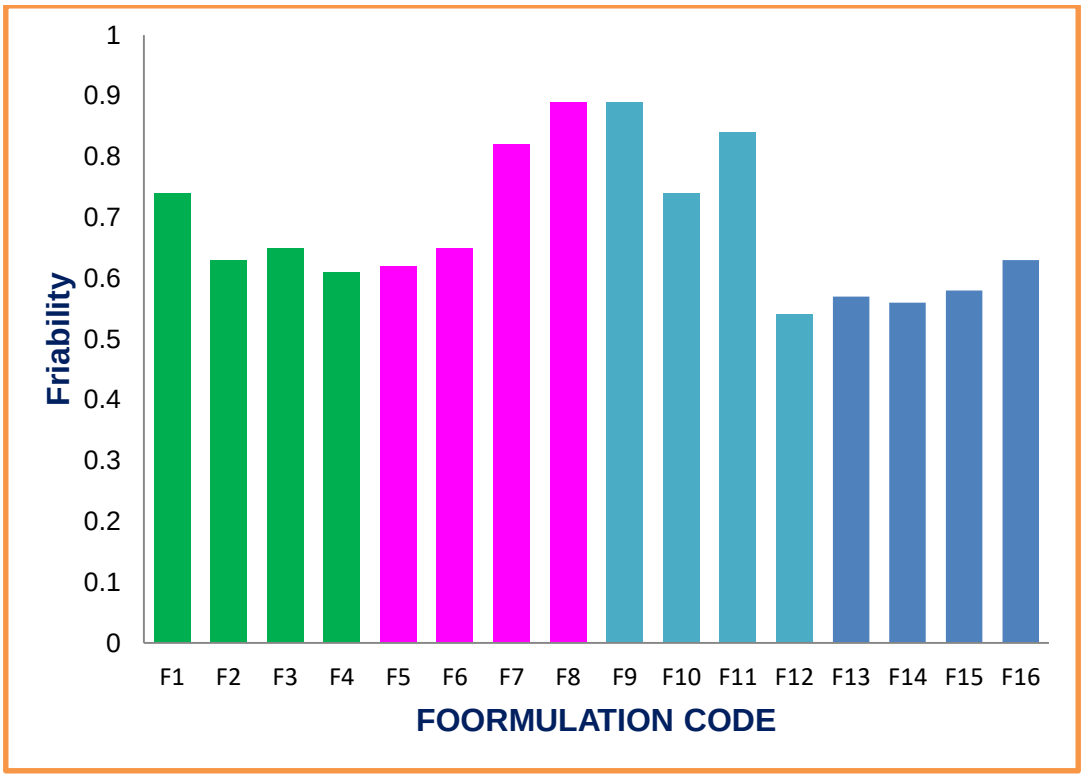


**FIGURE: 9A INVITRO DRUG RELEASE OF LYMECYCLINE CHEWING GUM WITH PVA AT DIFFERENT CONCENTRATIONS**

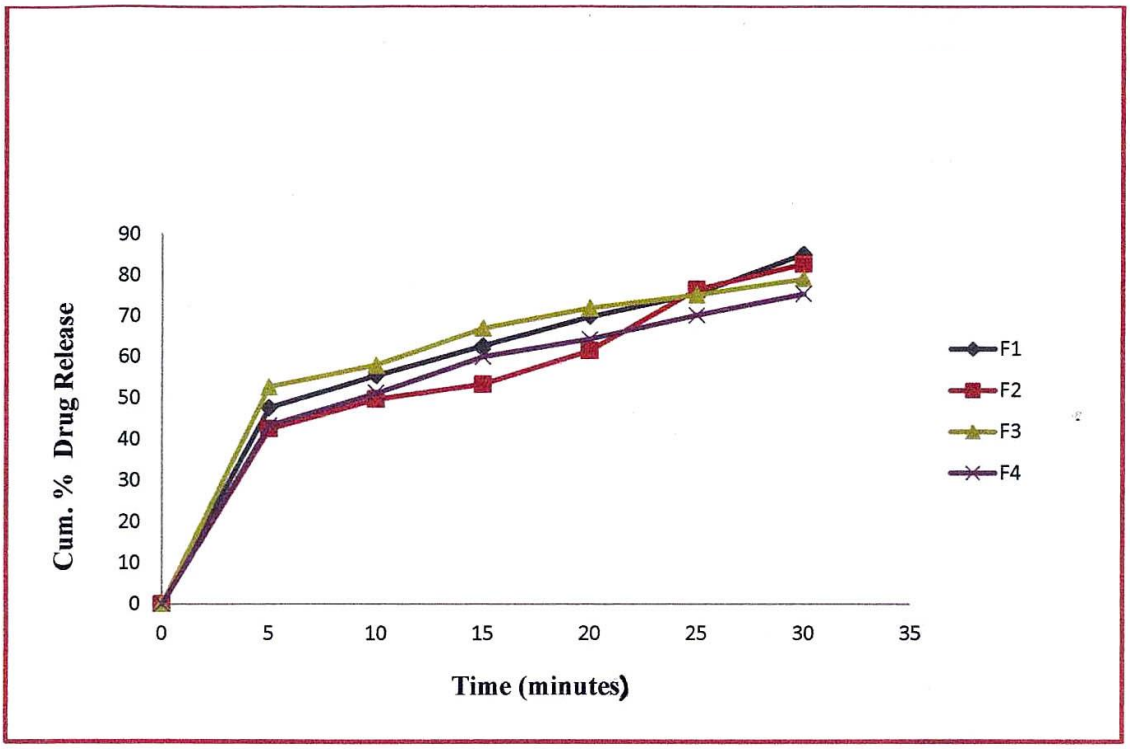



**FIGURE: 9B INVITRO DRUG RELEASE OF LYMECYCLINE CHEWING GUM WITH β-CD AT DIFFERENT CONCENTRATIONS**

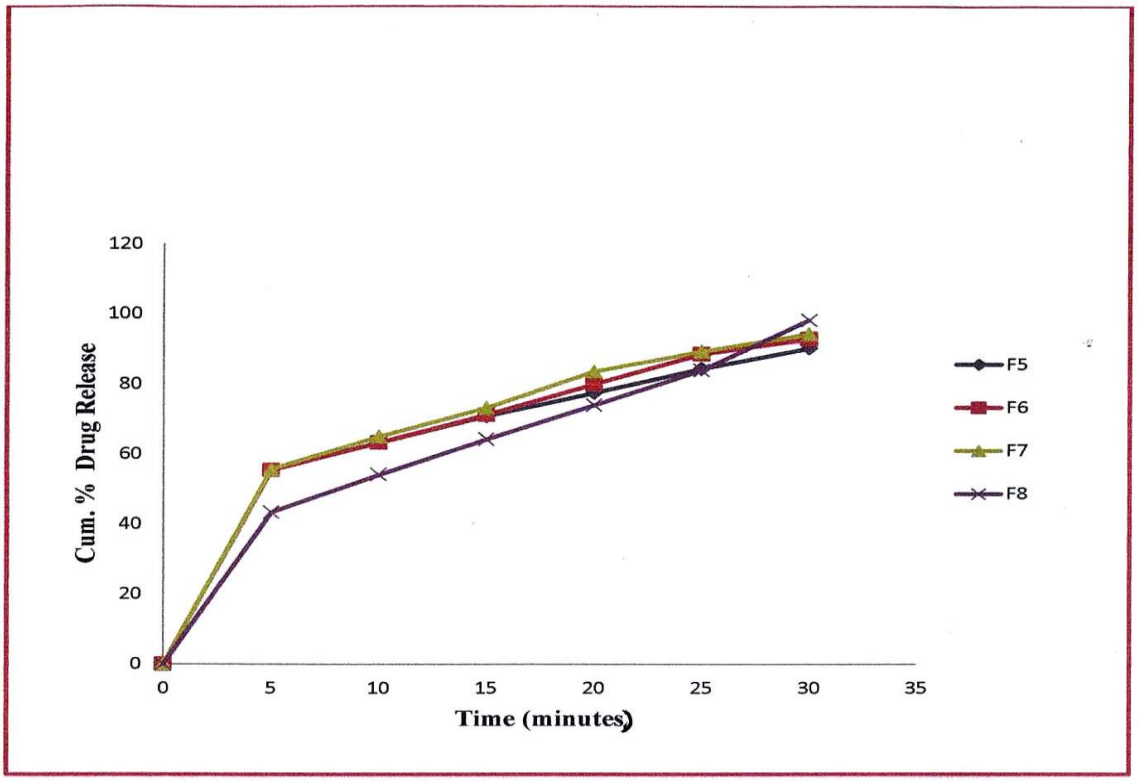


FIGURE: 9C INVITRO DRUG RELEASE OF LYMECYCLINE CHEWING GUM WITH PEG AT DIFFERENT CONCENTRATIONS

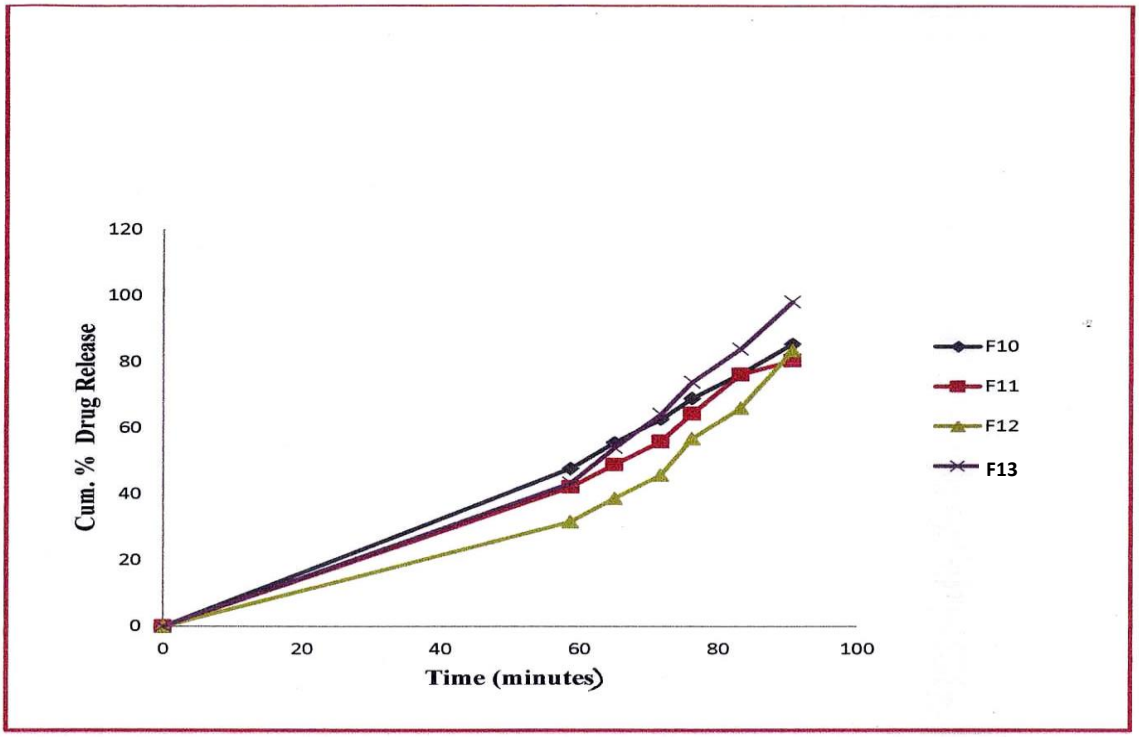



FIGURE: 9D INVITRO DRUG RELEASE OF LYMECYCLINE CHEWING GUM WITH CROS POVIDONE AT DIFFERENT CONCENTRATIONS

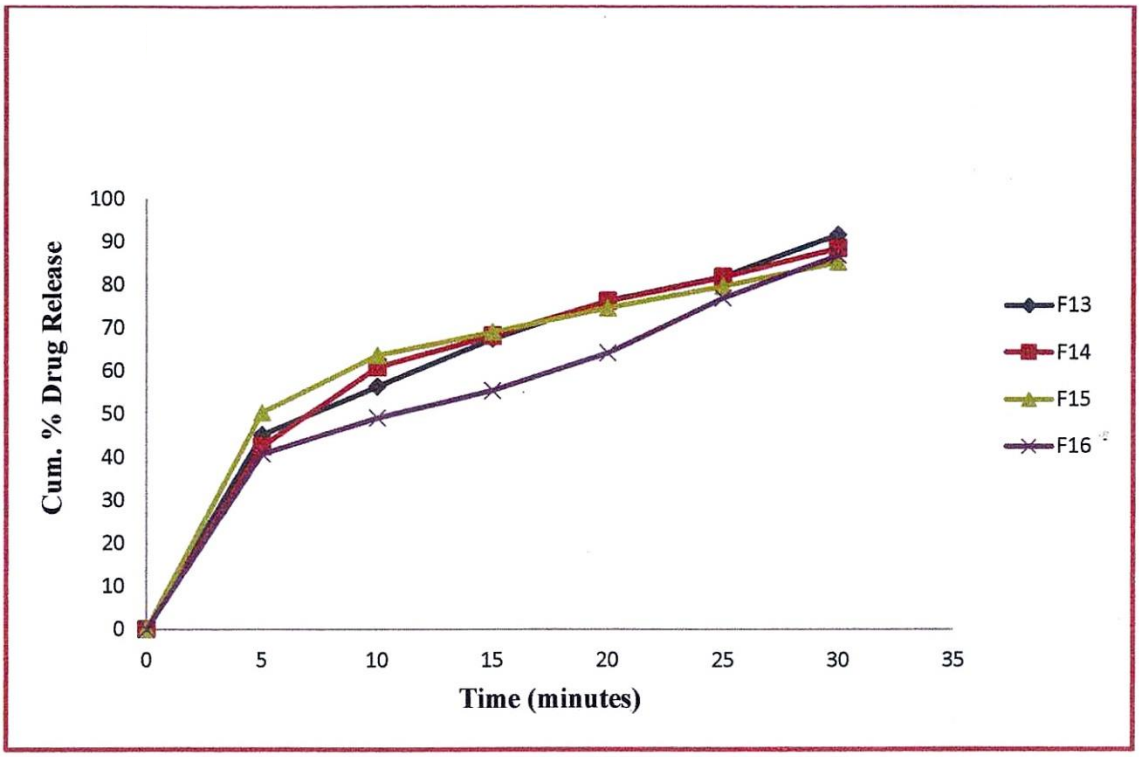


**FIGURE: 10A COMPARISION OF INVITRO DRUG RELEASE PROFILE OF LYMECYCLINE MEDITATED CHEWING GUM CONTAINING PVA AT DIFFERENT RATIOS**

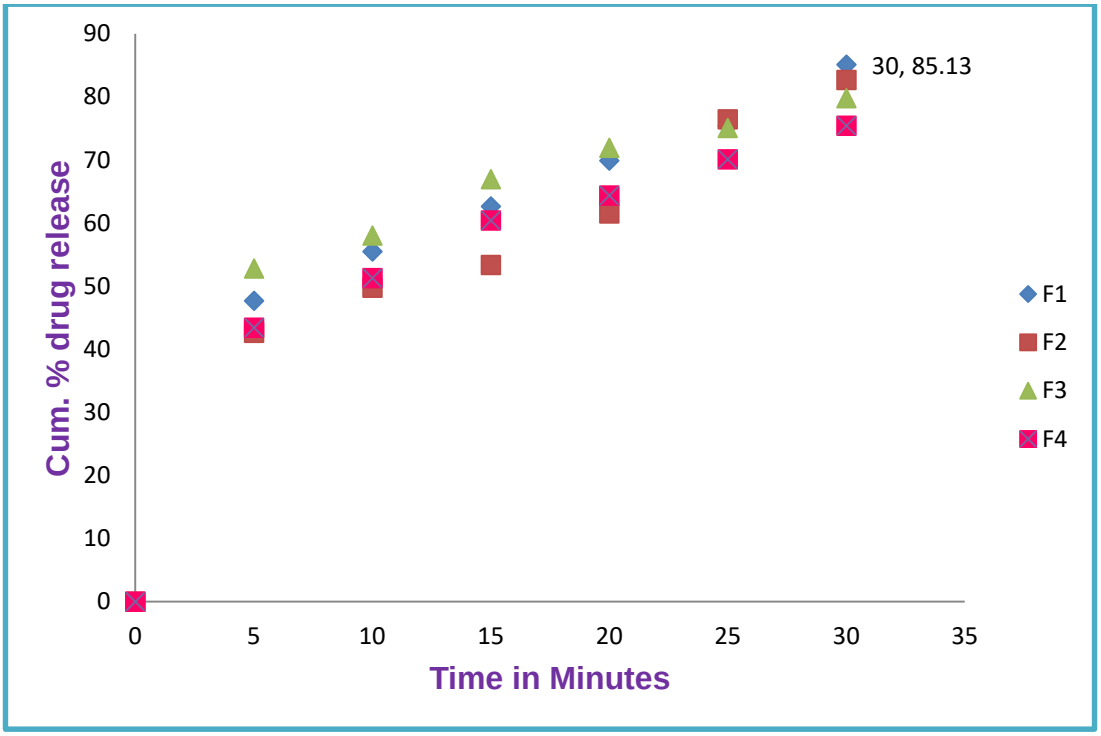



**FIGURE: 10B COMPARISION OF INVITRO DRUG RELEASE PROFILE OF LYMECYCLINE MEDITATED CHEWING GUM CONTAINING β-CD AT DIFFERENT RATIOS**

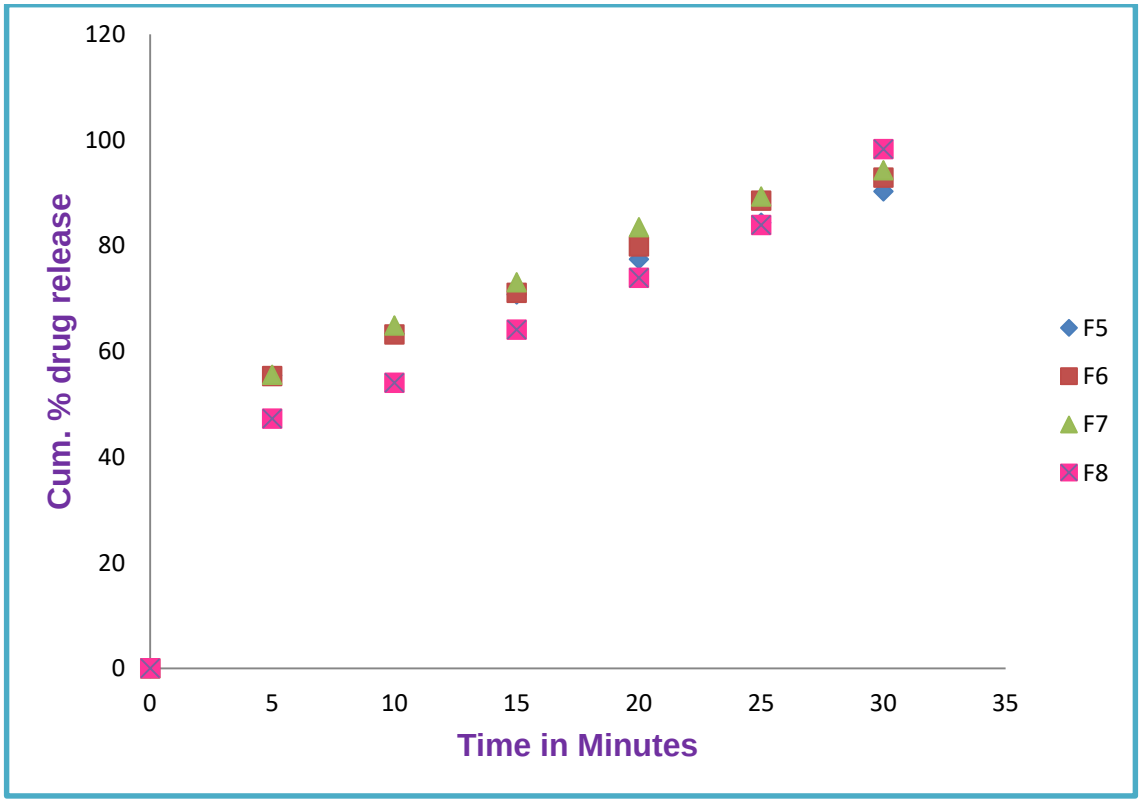


**FIGURE: 10C COMPARISION OF INVITRO DRUG RELEASE PROFILE OF LYMECYCLINE MEDITATED CHEWING GUM CONTAINING PEG AT DIFFERENT RATIOS**

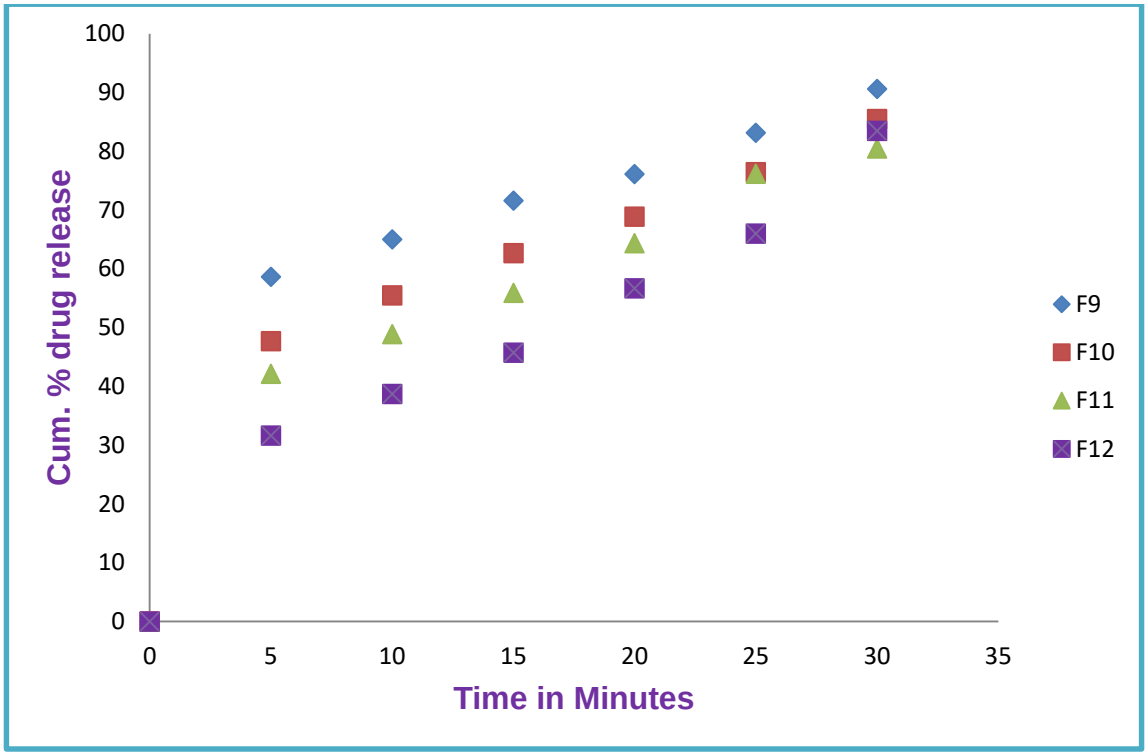



**FIGURE: 10D COMPARISION OF INVITRO DRUG RELEASE PROFILE OF LYMECYCLINE MEDITATED CHEWING GUM CONTAINING CROS POVIDONE AT DIFFERENT RATIOS**

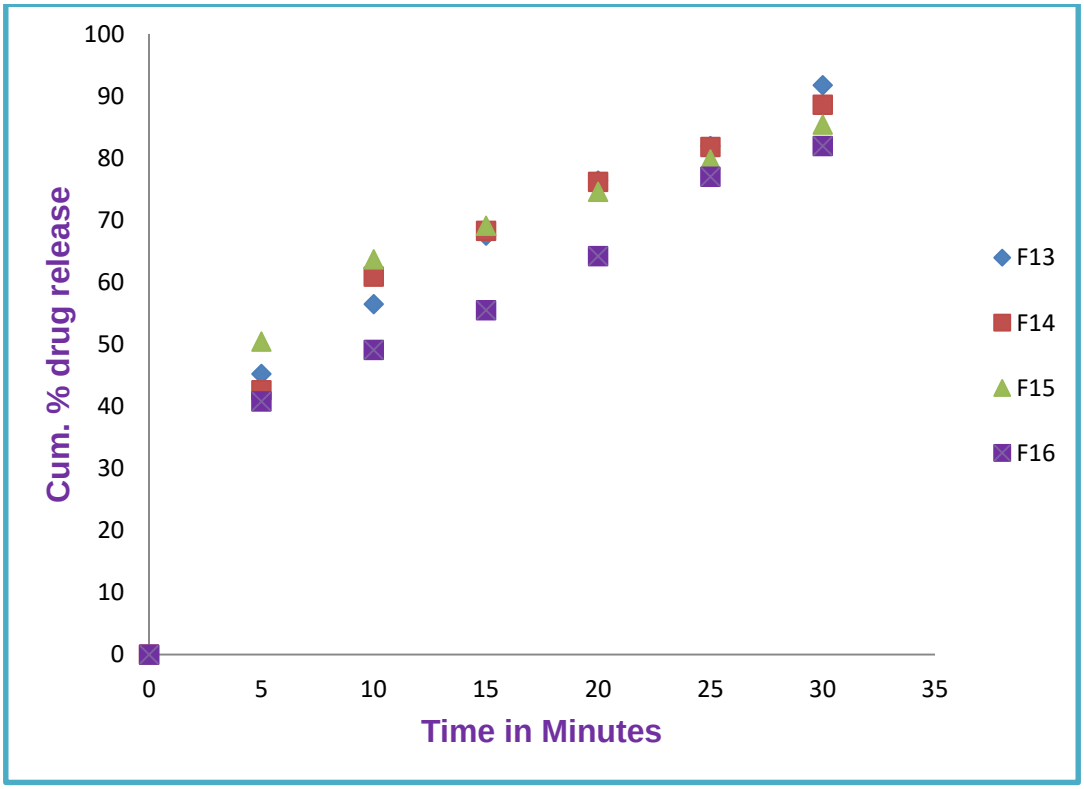


FIGURE: 11A COMPARISION OF INVITRO FIRST ORDER KINETICS OF LYMECYCLINE- PVA MEDICATED CHEWING GUM

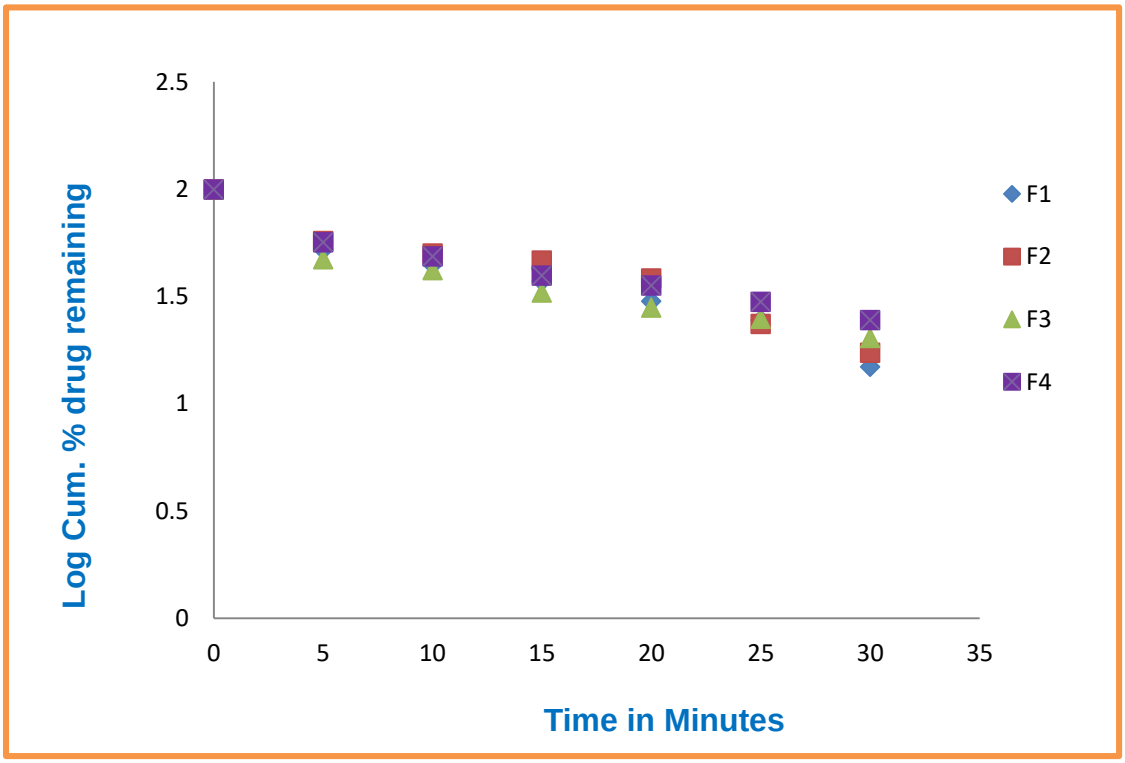



FIGURE: 11B COMPARISION OF INVITRO FIRST ORDER KINETICS OF LYMECYCLINE- β-CD MEDICATED CHEWING GUM

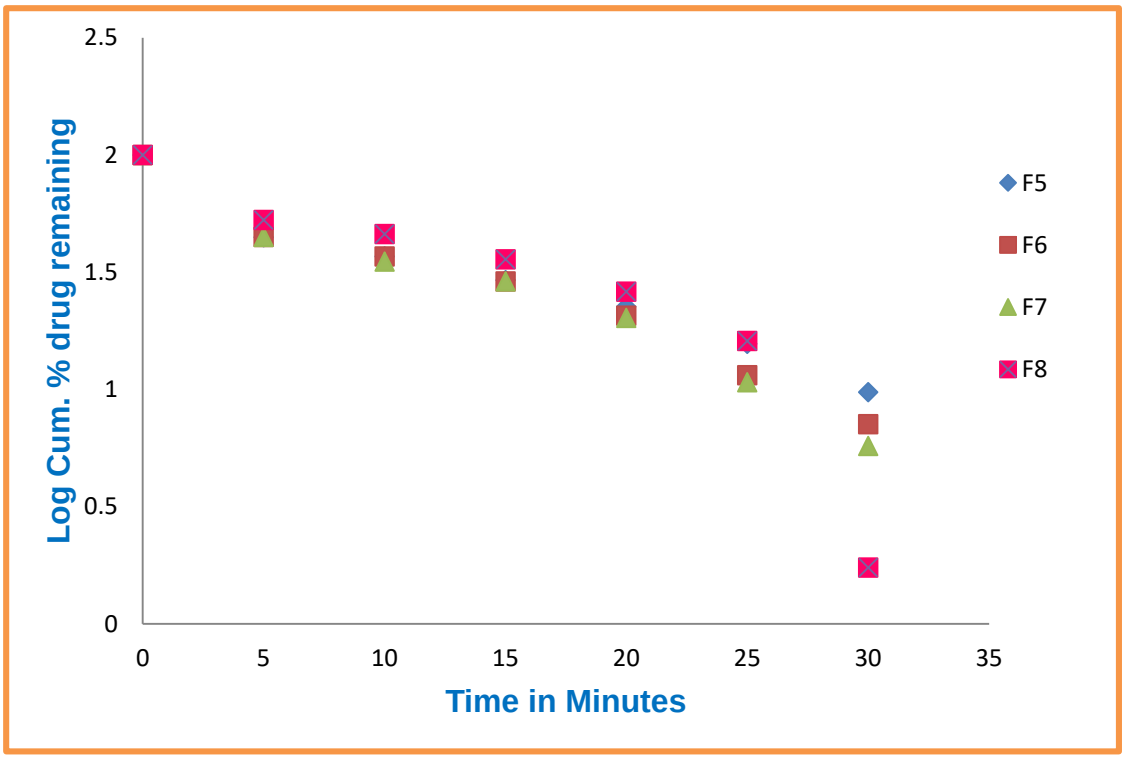


FIGURE: 11C COMPARISION OF INVITRO FIRST ORDER KINETICS OF LYMECYCLINE- PEG MEDICATED CHEWING GUM

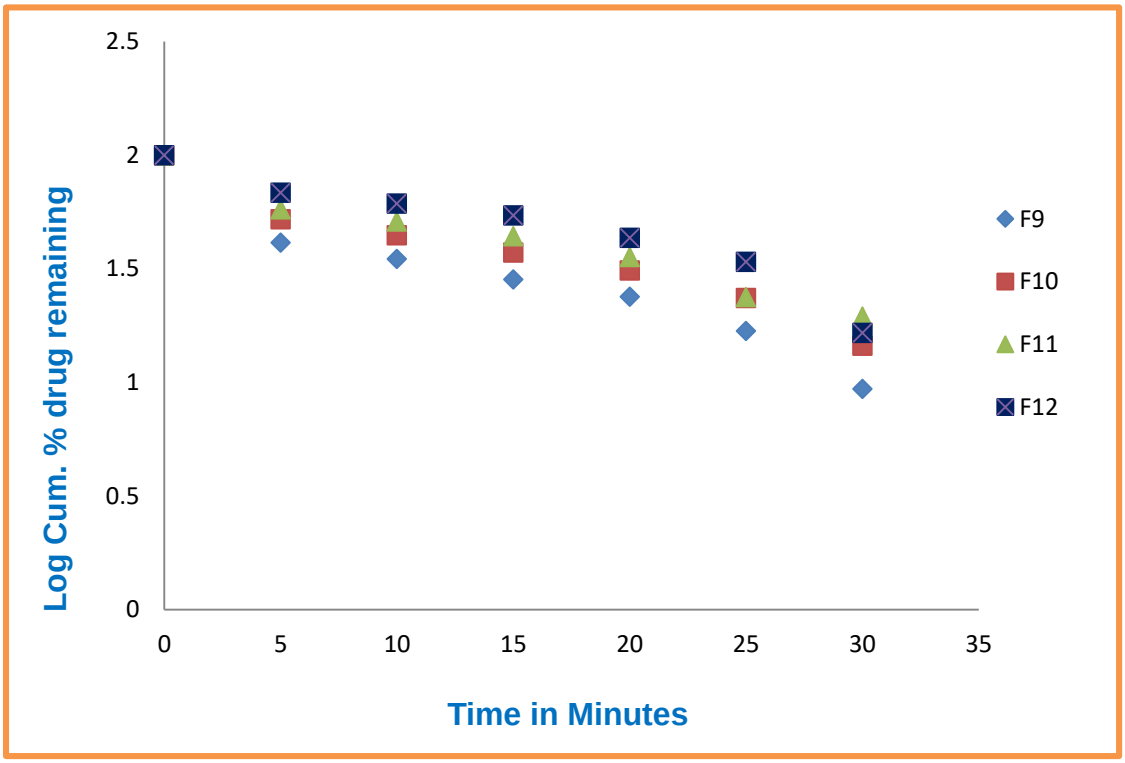



FIGURE: 11D COMPARISION OF INVITRO FIRST ORDER KINETICS OF LYMECYCLINE- CROS POVIDONE MEDICATED CHEWING GUM

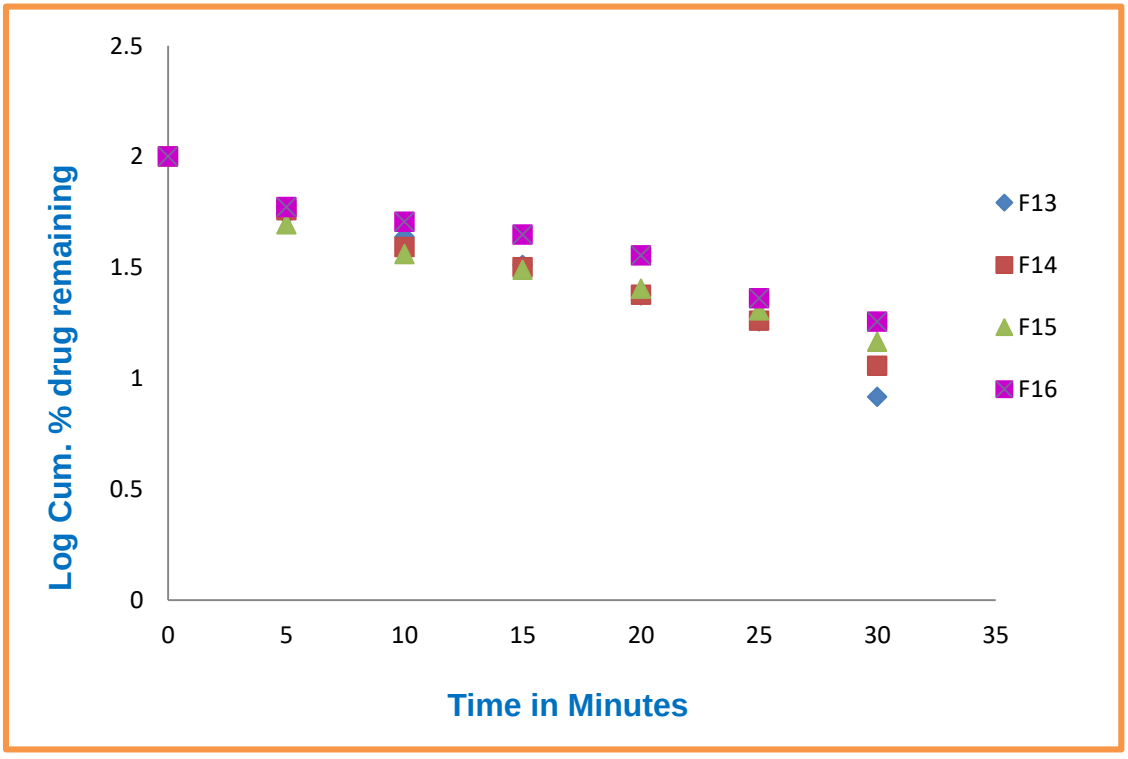


FIGURE: 12A COMPARISION OF INVITRO KORES-MEYER KINETICS OF LYMECYCLINE- PVA MEDICATED CHEWING GUM

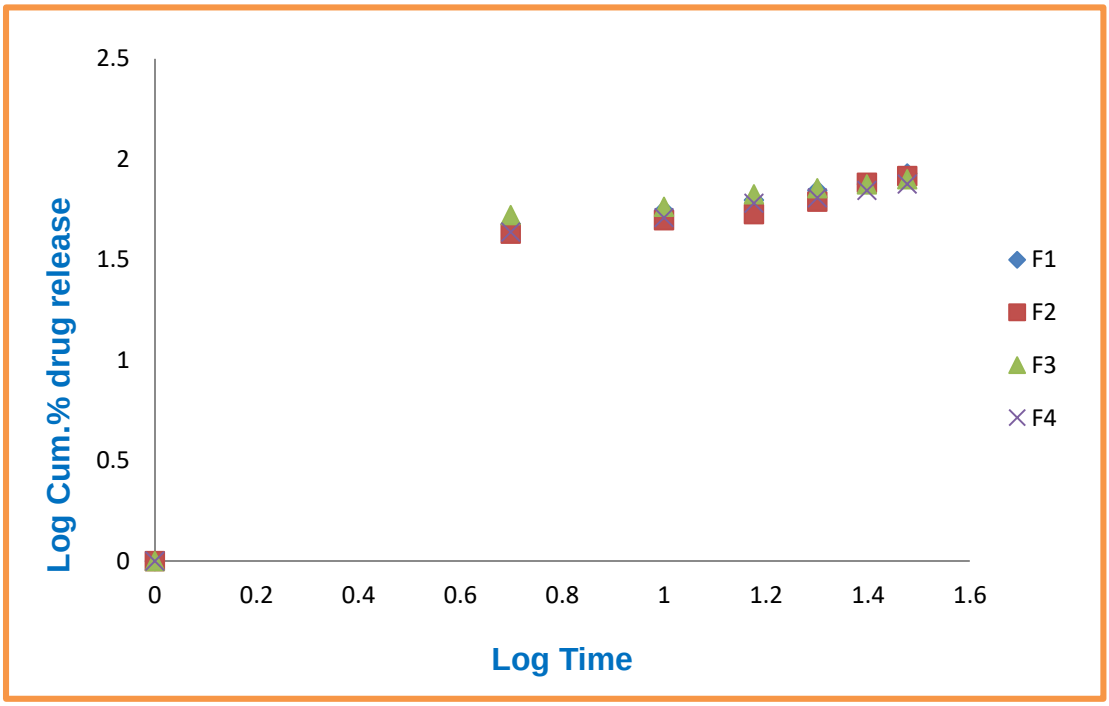



FIGURE: 12B COMPARISION OF INVITRO KORES-MEYER KINETICS OF LYMECYCLINE- β-CD MEDICATED CHEWING GUM

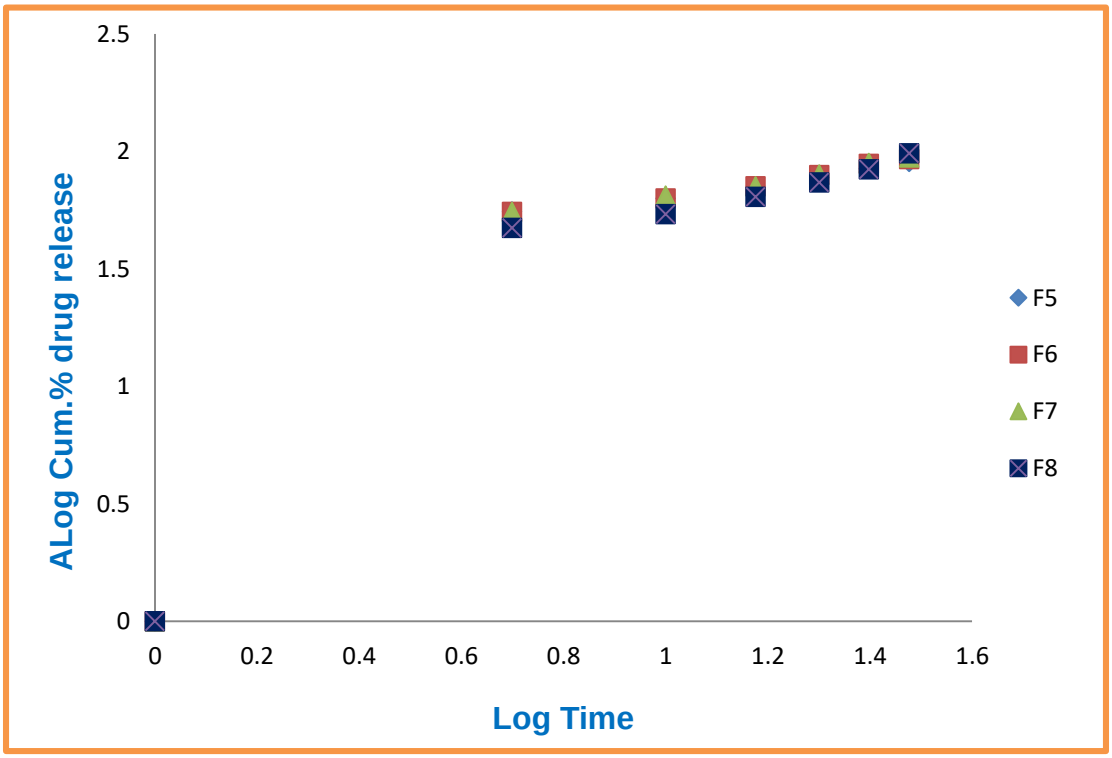


**FIGURE: 12C COMPARISION OF INVITRO KORES-MEYER KINETICS OF LYMECYCLINE- PEG MEDICATED CHEWING GUM**

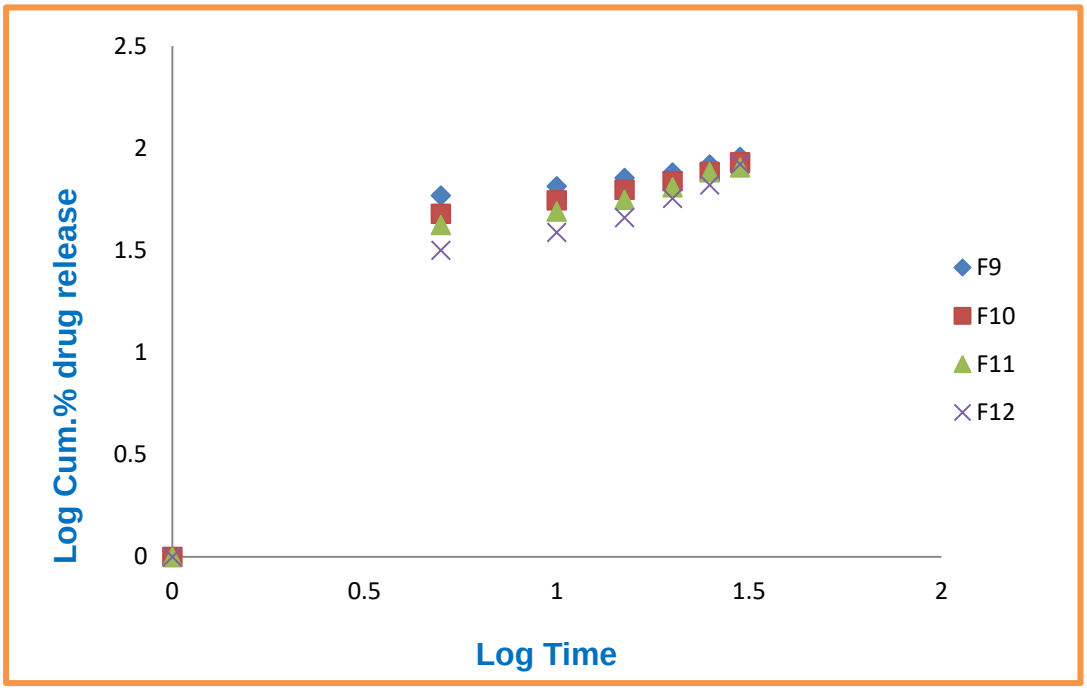



**FIGURE: 12D COMPARISION OF INVITRO KORES-MEYER KINETICS OF LYMECYCLINE- CROS POVIDONE CHEWING GUM**

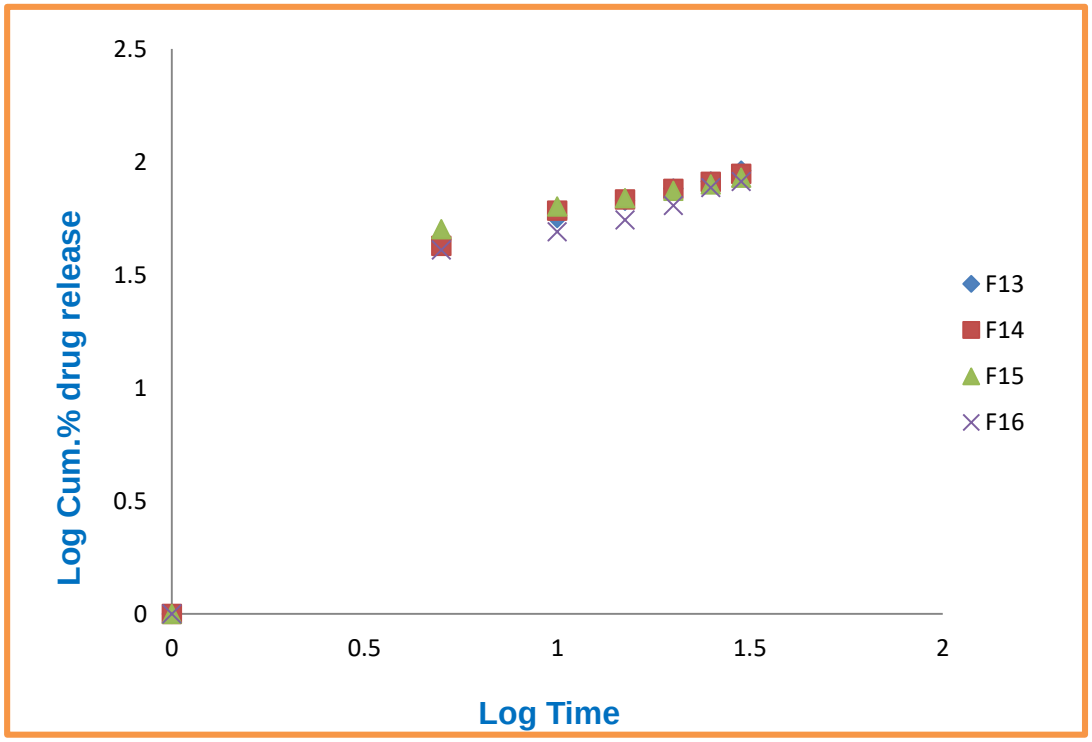


FIGURE: 13A COMPARISION OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF LYMECYCLINE- PVA MEDICATED CHEWING GUM

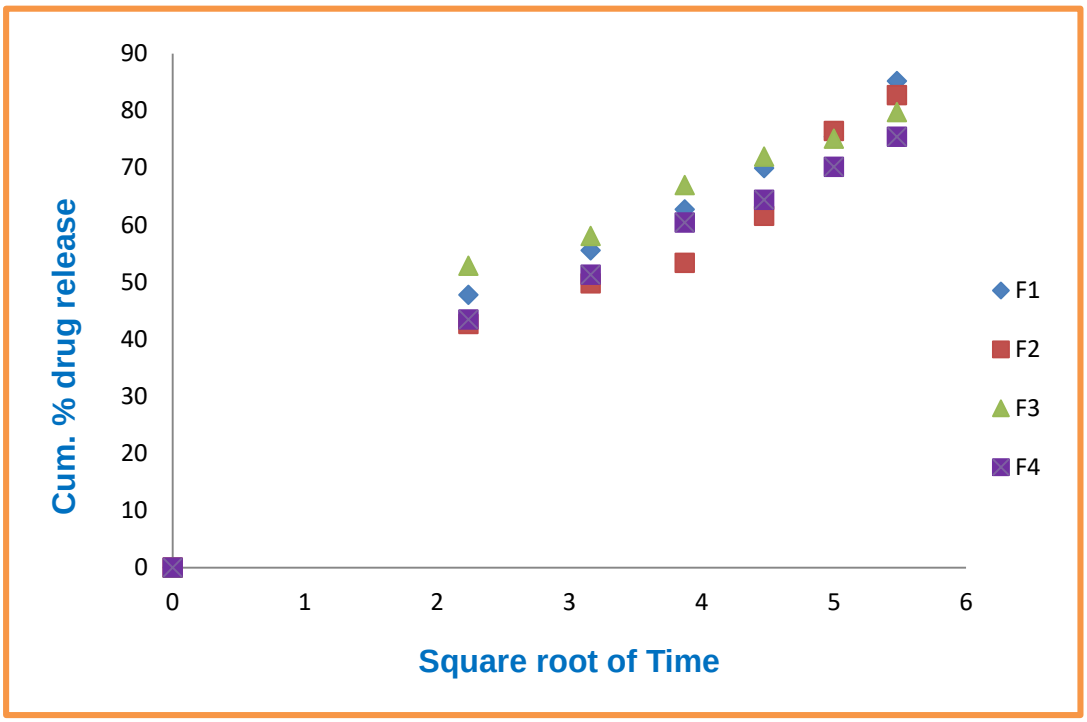



FIGURE: 13B COMPARISION OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF LYMECYCLINE- β-CD MEDICATED CHEWING GUM

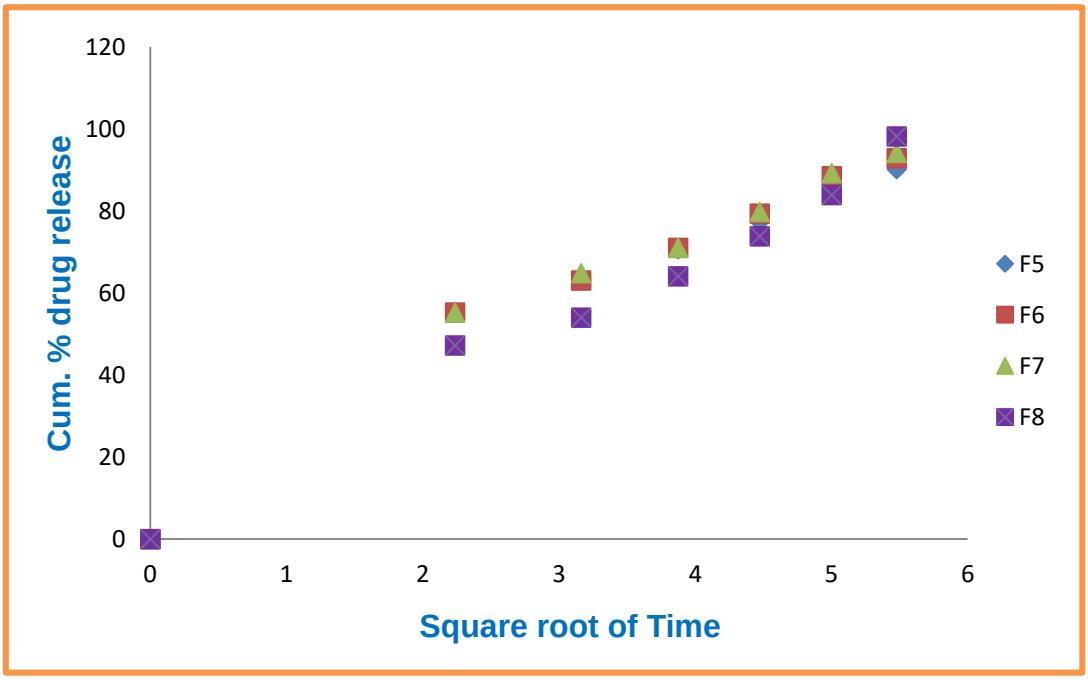


FIGURE: 13C COMPARISION OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF LYMECYCLINE- PEG MEDICATED CHEWING GUM

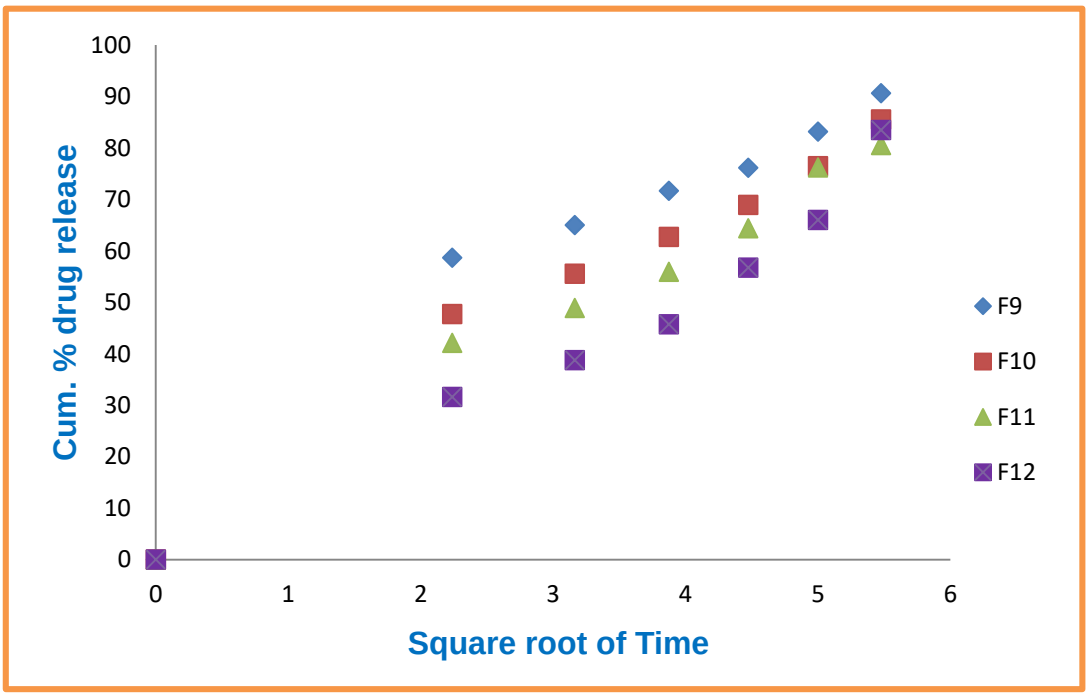



FIGURE: 13D COMPARISION OF INVITRO HIGUCHI MODEL RELEASE KINETICS OF LYMECYCLINE- CROS POVIDONE MEDICATED CHEWING GUM

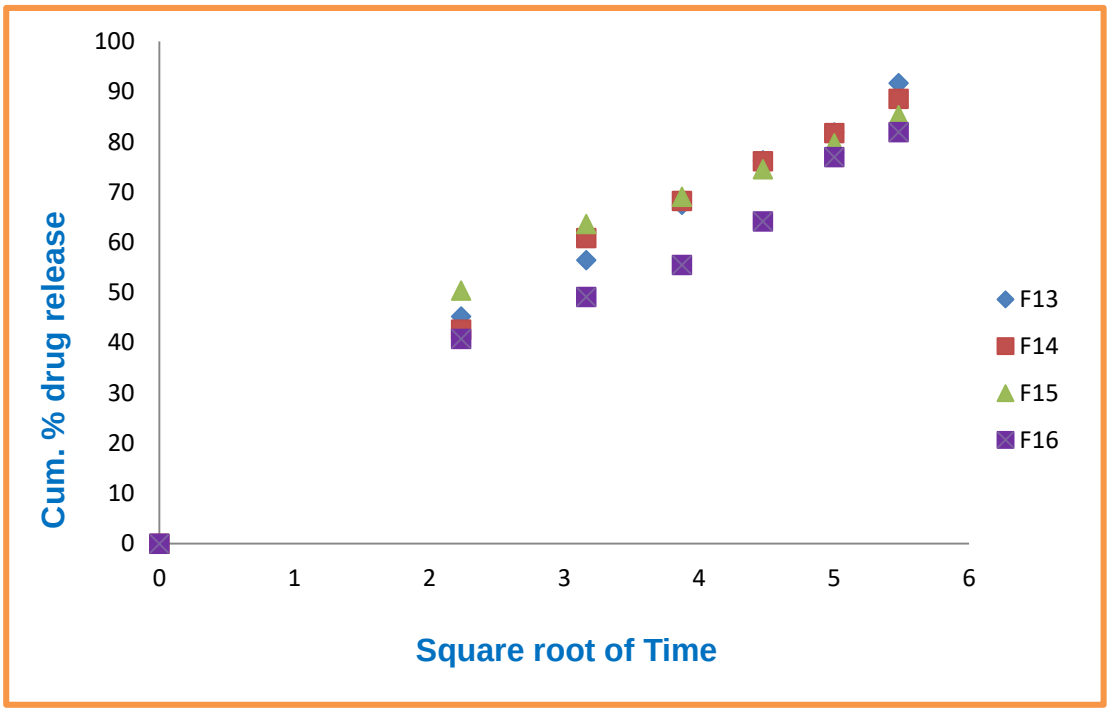


FIGURE: 14A COMPARISION OF INVITRO HIXON CROWELL MODEL RELEASE KINETICS OF LYMECYCLINE- PVA MEDICATED CHEWING GUM

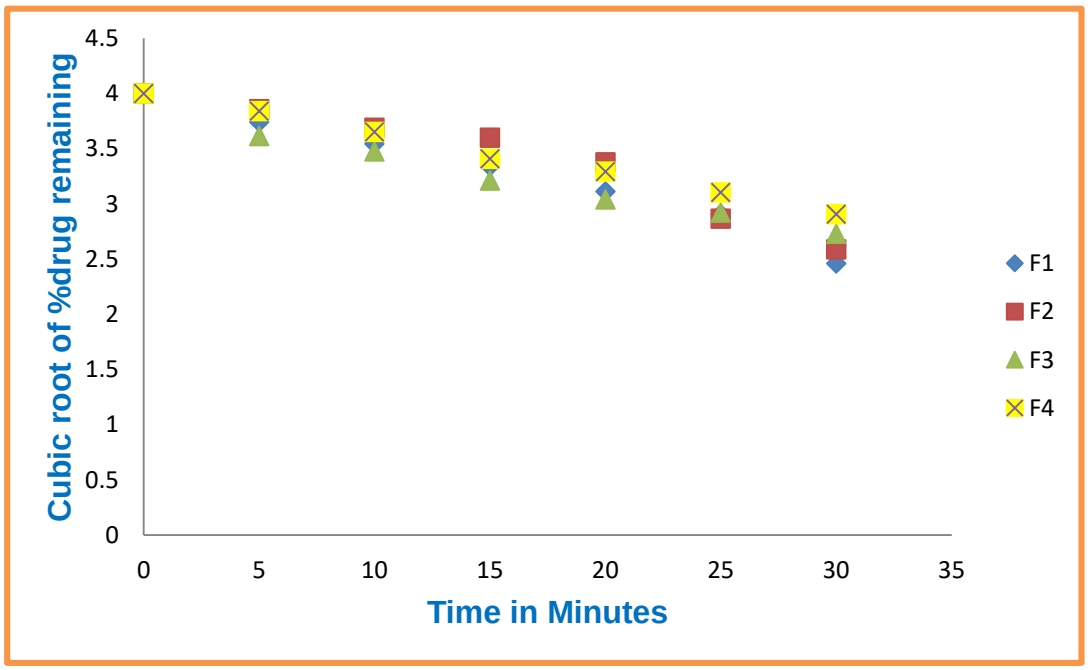



FIGURE: 14B COMPARISION OF INVITRO HIXON CROWELL MODEL RELEASE KINETICS OF LYMECYCLINE- β-CD MEDICATED CHEWING GUM

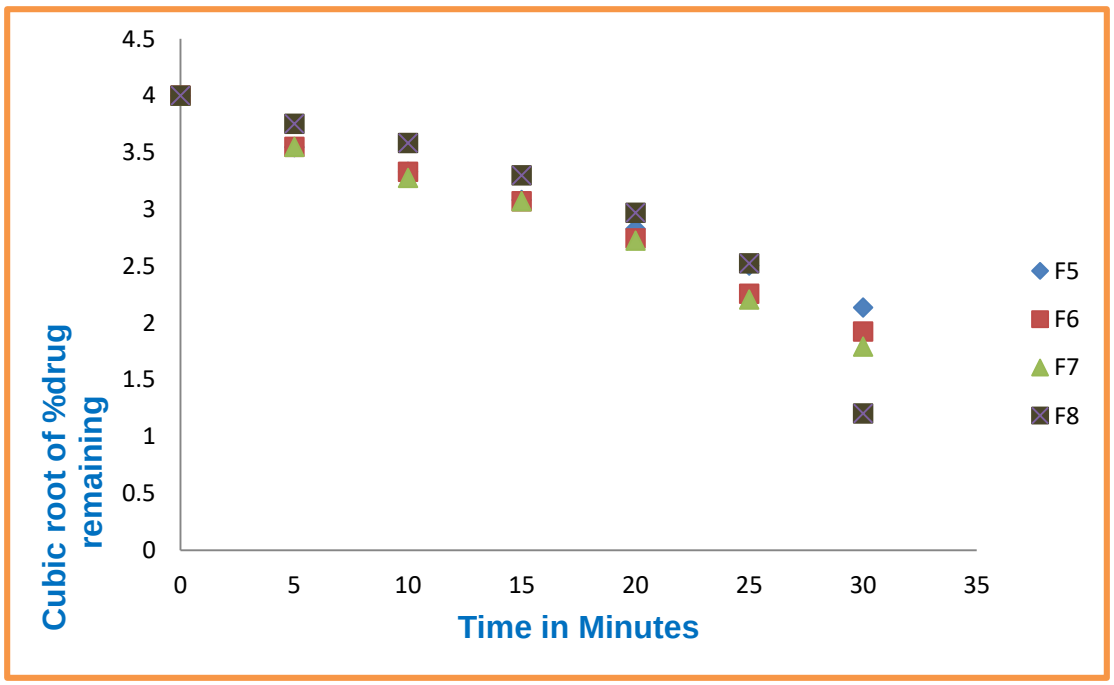


FIGURE: 14C COMPARISION OF INVITRO HIXON CROWELL MODEL RELEASE KINETICS OF LYMECYCLINE- PEG MEDICATED CHEWING GUM

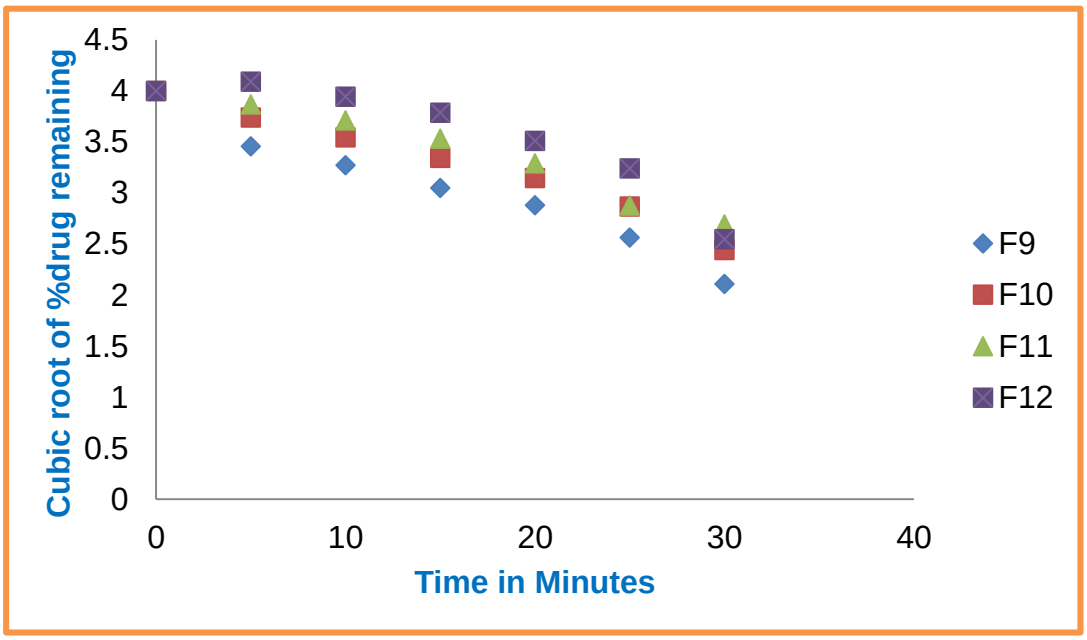



FIGURE: 14D COMPARISION OF INVITRO HIXON CROWELL MODEL RELEASE KINETICS OF LYMECYCLINE- CROS POVIDONE MEDICATED CHEWING GUM

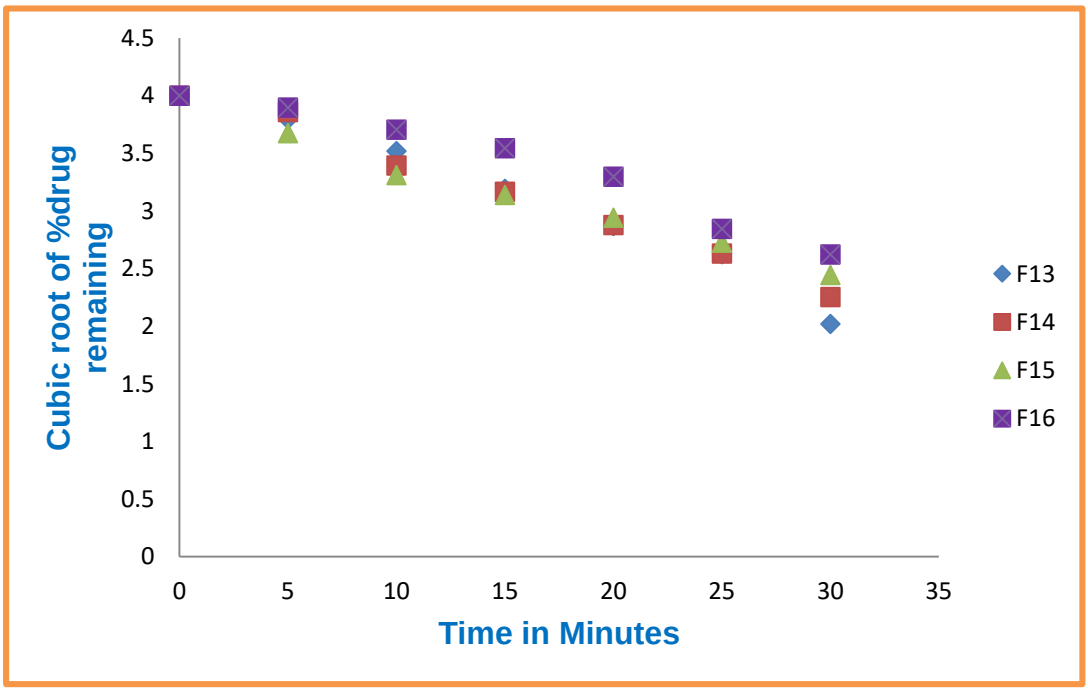


**FIGURE 15: FTIR SPECTRUM OF BEST FORMULATION F8 (β-CD) MEDICATED CHEWING GUM**

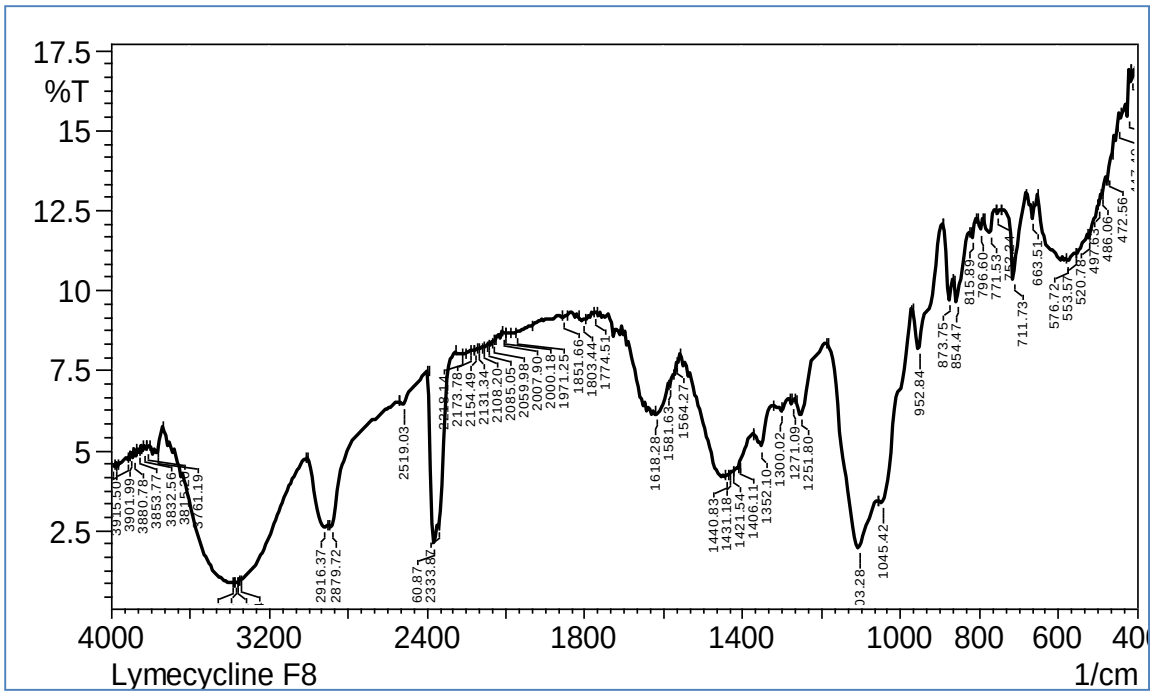
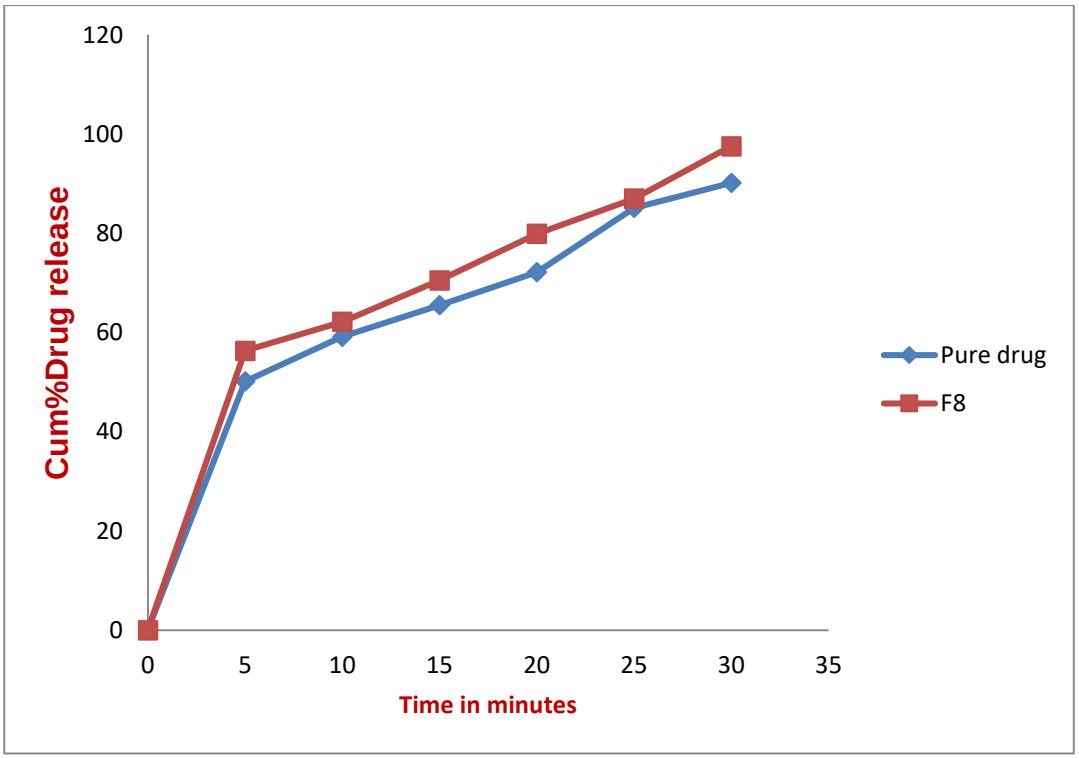
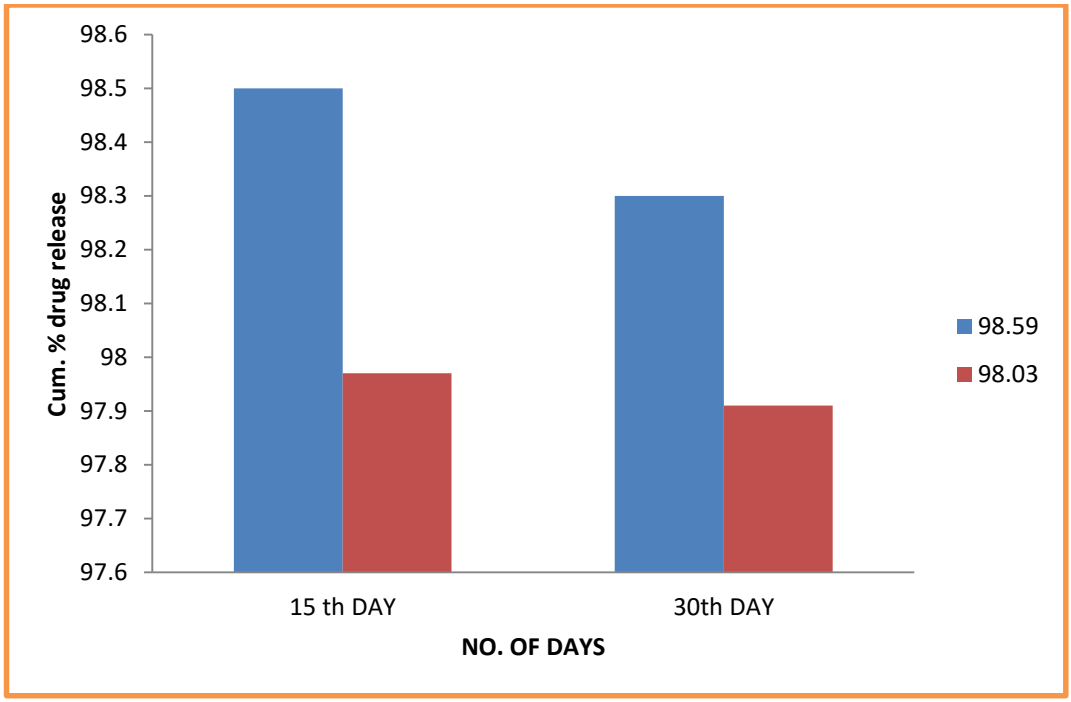


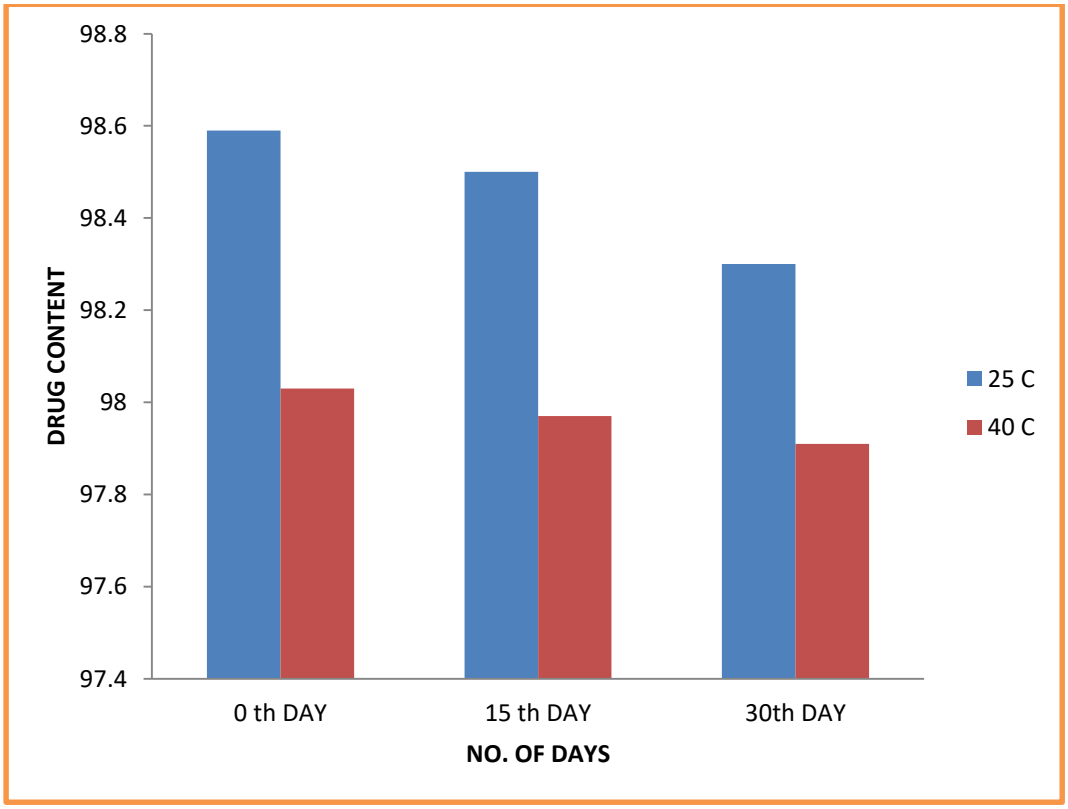

**FIGURE 16: INVITRO RELEASE PROFILE OF LYMECYCLINE PURE DRUG AND BEST FORMULATION (F8)**



## FIGURE 17: INVITRO DRUG RELEASE PROFILEOF BEST FORMULATION (F8)




## FIGURE 18: DRUG CONTENT OF BEST FORMULATION (F8)



## FIGURE: 19 DSC STUDIES OF BEST FORMULATION (F8)

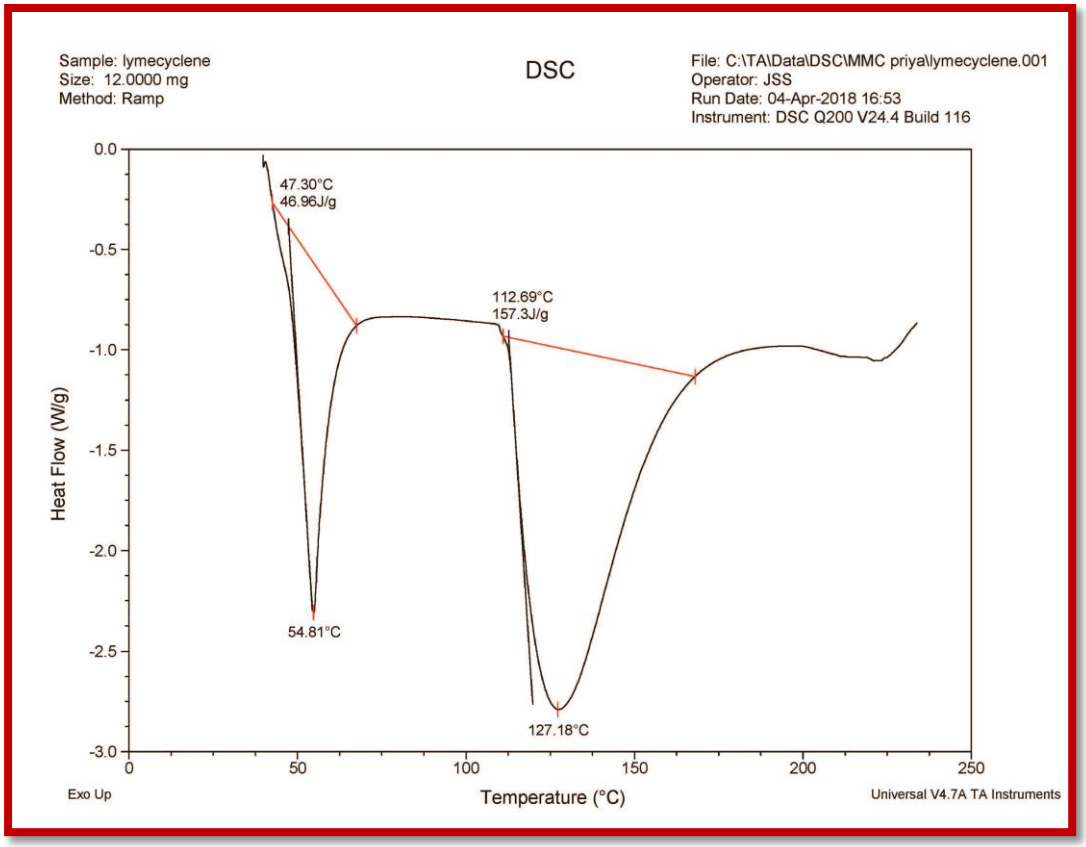
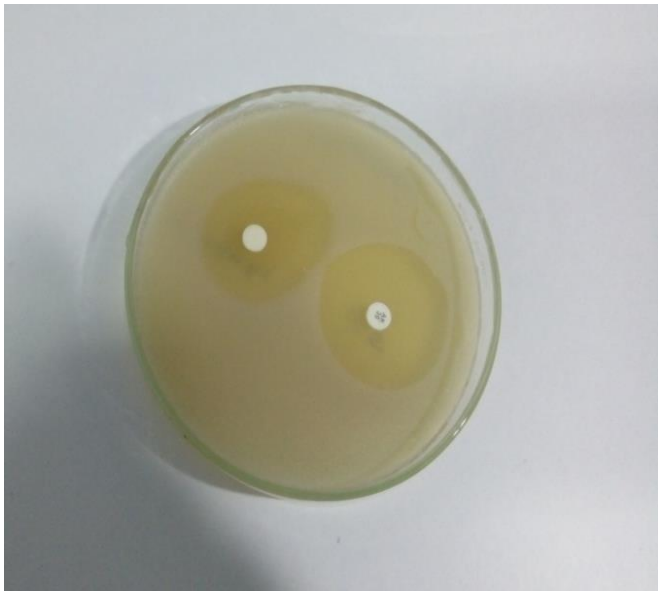
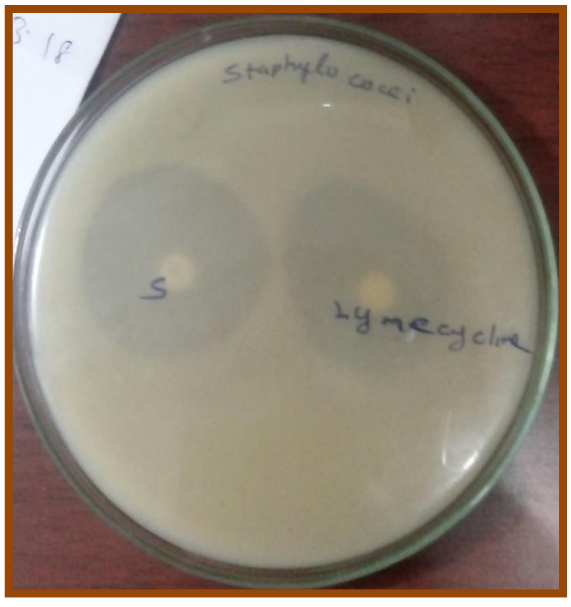


**FIGURE: 20 ANTIBACTERIAL ACTIVITY OF LYMECYCLINE CHEWING GUM BY DISC DIFFUSION METHOD**



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Dr. S. PURATCHIMANI, MBBS., M.Sc.,(Micro), Founder & Chairman
Dr. S. P. ARIVARASAN, M.D.(PATH) Medical Director 9994277777
Dr. A. KOMAGAL, MBBS., Deputy Medical Director

## LABORATORY REPORT

| SAMPLE CODE (LYMECYCLINE) | STREPTOCOCCI | STPHYLOCOCCI |
|---|---|---|
| LYME | 15MM | 14MM |
| STANDARD DISC | 20MM | 20MM |

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# CHAPTER XI

# SUMMARY AND CONCLUSION

# CHAPTER-XI

# SUMMARY AND CONCLUSION

- In the present study, an attempt has been made to formulate medicated chewing gum of lymecycline to achieve better patient compliance and improved drug release.
- The results of compatibility studies by infrared spectroscopy and differential scanning colorimetric (DSC), showed no interaction between the drug and stabilizers.
- Medicated chewing gum of Lymecycline were successfully prepared by melting method using different concentrations of polymers, PVA, BCD, PEG-4000, cros povidone and without polymers.
- The presence of polymers made the chewing gum more stable with increasing drug release.
- Plasticizer ratio and synthetic gum base concentration are critical parameters which affect the consistency and drug release profile.
- The Drug content of the selected formulations (F8) was 98.03%, which indicates the maximum amount of drug present in the formulation chewing gum.
- In Vitro release study of all the formulations were showed in increase drug release with increase in concentration of polymers (PVA, PEG-4000 ,β-CD, Cros Povidone ) Dissolution rate of all the formulations were improved when compared to pure drug.

- The dissolution study was carried out in $P^H$ 6.8 phosphate buffer for 30 minutes. The formulations shows rapid release of drug in 20 minutes & all formulations showed more than 90% of drug release.
- Medicated chewing gum consisted mainly of calcium carbonate and gum base showed good elasticity, chew ability and satisfactory drug release.
- The selected best formulation was tested for its antibacterial activity.
- Chewing gum (Lymecycline) showed increased with Lymecycline capsules.
- The faster onset of action desired in delivery of indicated chewing gum.
- In all the formulations, F8 shows highest drug release of in 30 minutes.
- The invitro release studies revealed that the prepared chewing gums showed a faster drug release when compared to the pure drug.
- The formulations are kept for accelerated stability studies; they showed no change in the drug release profile. Thus stability results prove that the formulation was stable at accelerated conditions.

**Conclusion:**

- Hence, it was concluded that Medicated chewing gum of lymecycline was successfully prepared by melting method using different concentrations of plasticizer and synthetic gum base, Formula is optimized by changing the plasticizer ratio and synthetic gum base concentration are critical parameters which effect the consistency and drug release profile. Based on the drug release files of all the formulations, formulation F8 is the

optimized formulations are kept for stability studies. Thus, it's the better option to prepare Lymecycline into a medicated chewing gum to achieve better patient compliance and improved drug release.

- From this study it was concluded that chewing gum that contains highest amount of β-cyclodextrin showed good release in invitro studies. It indicates that B-cyclodextrin acts as a good solubilizer which enhances the solubility of the drug Lymecycline. Higher polymer ration enhances drug solubility, which leads to increase in the amount of drug absorption. By delivering Lymecycline in the form of chewing gum, it directly enters into systemic circulation thus by passes first pas metabolism and hence bio availability of drug increase.

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# REFERENCES


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